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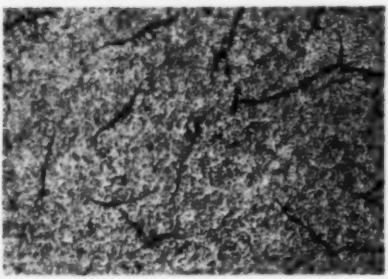
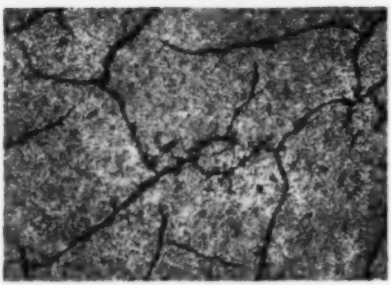
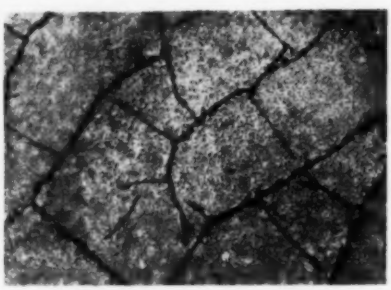
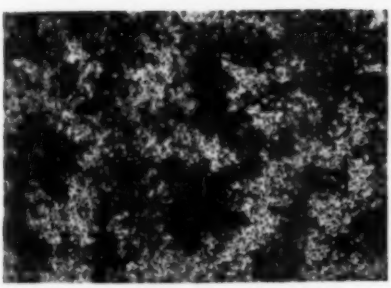




preventing clot formation





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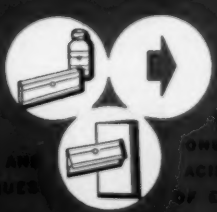

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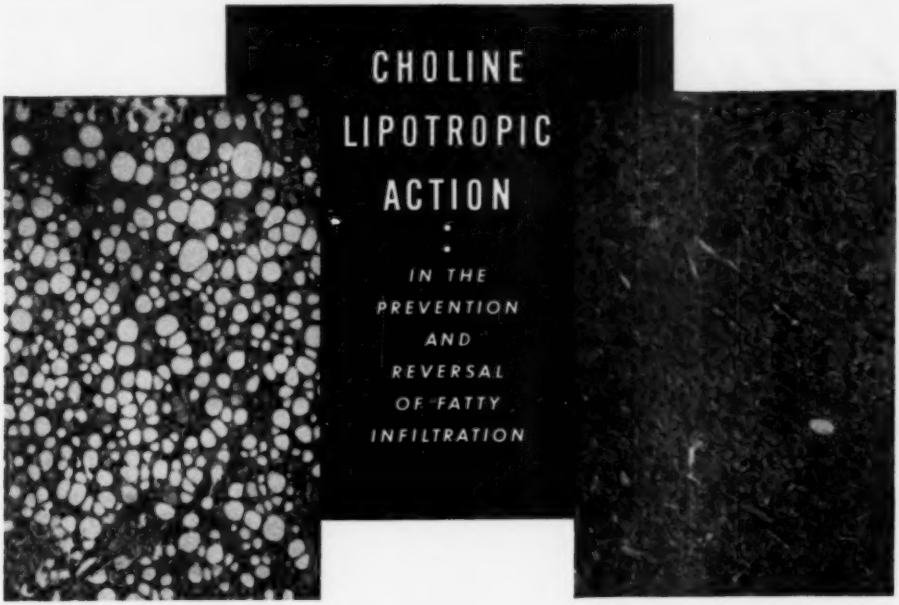

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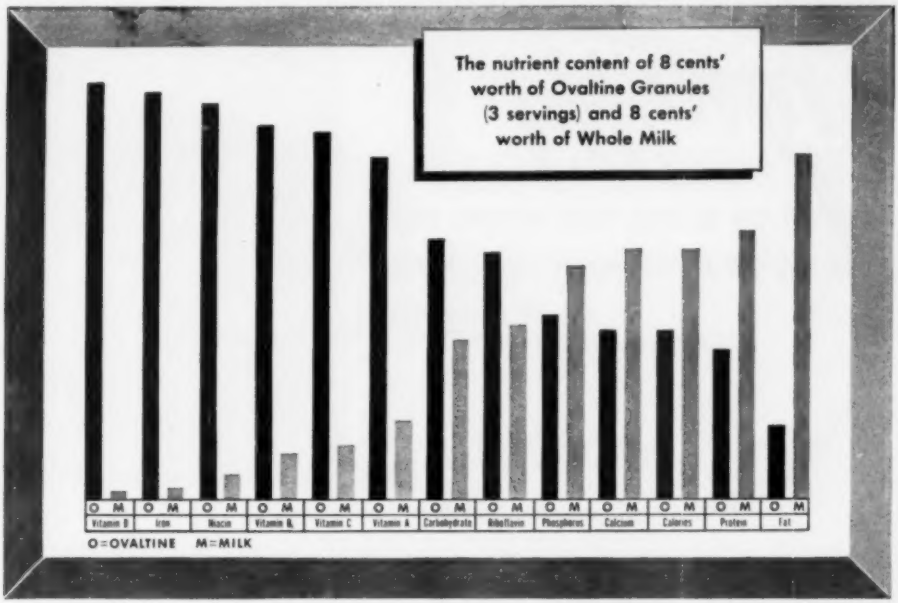

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ANNALS OF
INTERNAL MEDICINE

VOLUME 33 DECEMBER, 1950 NUMBER 6

THE INTERNIST'S NUMBER ONE PROBLEM—CHRONIC DISEASE IN AN AGING POPULATION *

By HOWARD A. RUSK, M.D., F.A.C.P., *New York, N. Y.*

IN the minds of most internists, physical medicine and rehabilitation is a medical specialty which is primarily applicable to the specialties of orthopedics, surgery and neurology, but which lacks a close relationship to internal medicine. Until the last few years this concept was somewhat justified, for physical medicine was largely concerned with the passive application of light, heat, water and massage, and, although widely used in the treatment of peripheral vascular diseases, arthritis and other disorders of particular interest to internists, the greater emphasis was placed upon orthopedic and neurologic conditions.

During the past few years, however, there has developed a new concept of physical medicine and rehabilitation in which emphasis is placed not only on reducing the physical disability of the patient, but upon retraining the permanently disabled patient to live and to work as effectively as possible with those remaining physical capacities which he possesses.

The development of this new concept of dynamic therapeutics through rehabilitation had its genesis in the wartime programs for disabled servicemen. The need is now accentuated by the growing incidence of chronic disease resulting from an aging population. Lacking specifics to cure many of the chronic diseases, medicine must look to rehabilitation to teach the chronically disabled to live within the limits of their disabilities but to the hilt of their capabilities.

It is in the area of chronic disease that physical medicine and rehabilitation holds great implications for internal medicine, for probably three-quarters of the time of the average internist is spent on patients with chronic illness. The problems of acute, communicable disease that commanded our

* Presented at the Thirty-first Annual Session of the American College of Physicians, Boston, Massachusetts, April 21, 1950.

From the Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center.

major attention a few decades ago have been replaced by the problems of chronic illness. Ironically, it was the outstanding achievements of medicine during the past three decades that created our present problems: what to do with chronic disease and disability in our aging population.

Two thousand years ago, the average length of life was 25 years; at the turn of the century, it was 49; today it is nearly 67. In 1900, one person in 25 was 65 years of age or older; it is estimated that in 1980 the ratio will be one in 10. The chances today are two out of three that a young man now starting his working life at the age of 18 will live to his retirement age of 65, and the chances for a 55 year old man are 78 in 100.

There are a number of problems in the field of rehabilitation which are of particular interest to the internist.

Hemiplegia

It is estimated that there are more than a million individuals with hemiplegia in the United States, and the internist usually has been the first line of defense in their management. In the past, the attitude generally has been one of passive acceptance. Sedation, potassium iodide and psychotherapy, usually without too much conviction, have been the bases for management. With a dynamic approach to the problems of hemiplegia, much can be accomplished. As is the case with all patients who seek rehabilitation, it is necessary in dealing with the hemiplegic patient to exclude those cases in which the rehabilitation cannot keep up with the pathologic processes, as seen in the patient with malignant hypertension, or encephalomalacia, or advanced senility. Rehabilitation may safely be started with patients with moderate to severe hypertension if they are closely supervised and have adequate rest periods. It has been found that most patients will have a drop in pressure under a carefully regulated regime of mild activity and training. This is probably the result of the old axiom that "action absorbs anxiety."

The hemiplegic patient who is accepted for rehabilitation first must be given a careful physical examination, including the accepted studies of kidney and cardiac function and fundus grading. After such an examination, a muscle test is given to determine the power of both the affected and the unaffected muscles. Range of motion of joints is checked and noted. The heart of the rehabilitation evaluation from a functional standpoint is the activities of daily living test, a list of which follows. Each item measures one activity, such as the patient's ability to move from place to place in bed, to get from the bed to the wheelchair and back to bed, to dress and undress, and to comb the hair. This test can be administered by a therapist or a nurse and, with experience, is not too time-consuming.

There are two simple observations that assist markedly in the prognosis of the hemiplegic patient's ability to ambulate. If the patient is able freely to move the arm on the affected side, there is every reason to believe that he will be able to walk, since the arm is practically always more greatly affected

Physical Demands of Daily Life from Bed to Job

Date.....

Name.....Ward.....Age.....Sex.....

Address.....Apparatus.....

Cause.....Diagnosis.....

Disability.....Date Onset.....Date Referred.....

Method of Recording Test

☐ 1. If at the time of the initial testing an activity cannot be performed *independently*, leave the block blank.

☐ 2. If the activity can be performed *independently*, fill in the block with Blue pencil.

☐ 3. If the activity is not essential for the person's physical demands, draw diagonal lines in the block.

Method of Recording Progress

☐ 1. When the activity can be performed *independently*, fill in the block in Red and indicate the date of accomplishment.

I. *Non-Walking Activities*

		Date
A. *Bed Activities*		
1. Moving from place to place in bed		
2. Roll to right and then to left side		
3. Sitting erect in bed		
4. Turn and lie on abdomen		
5. Procure objects from night table		
B. *Hygiene (Toilet Activities)*		
1. Combing or brushing hair		
2. Brushing teeth		
3. Shaving or putting on cosmetics		
4. Washing hands and face		
5. Washing extremities		
6. Manipulating bed-pan		
7. Applying urinal/special pants		
8. Taking shower		
9. Tub bath		
10. Ability to dry self after shower or bath		
11. Adjusting clothing for toilet needs		
C. *Eating Activities*		
1. Cutting meat		
2. Buttering bread		
3. Eating with fork		
4. Eating with teaspoon, tablespoon		
5. Drinking from glass		
6. Drinking from cup		
7. Stirring coffee, tea, etc		
D. *Dressing and Undressing Activities*		
1. Put on underclothes		
2. Removing underclothes		
3. Put on buttoned shirt (zipper)		
4. Remove buttoned shirt		
5. Put on slip-over garment		
6. Remove slip-over garment		
7. Put on slacks		
8. Remove slacks		
9. Tying shoes (buckle, zipper)		
10. Tying tie		
11. Putting on hose		

PHYSICAL DEMANDS OF DAILY LIFE FROM BED TO JOB—*Continued*

			Date
D.	*Dressing and Undressing Activities (continued)*		
	12. Removing hose		
	13. Put on braces or prosthesis		
	14. Remove braces or prosthesis		
E.	*Hand Activities*		
	1. Write name and address		
	2. Fold letter, place in envelope and seal envelope		
	3. Open envelope, remove letter		
	4. Use dial telephone		
	5. Turn pages of book		
	6. Wind wrist watch		
	7. Open and close cylinder lock		
	8. Open and close ice box door		
	9. Open and close doorlock with key		
	10. Open and close drawers		
	11. Open and close door hooks		
	12. Open and close window		
	13. Pull window shade		
	14. Push door bell		
	15. Use workshop switch		
	16. Use work plug switch		
	17. Use work push button		
	18. Work key light switch		
	19. Work pull chain light		
	20. Ring door bell		
	21. Open and close cabinet lock		
	22. Turn 4-pronged faucet		
	23. Turn circular faucet		
	24. Open and close medicine chest		
	25. Open and close bottle		
	26. Open and close safety pin		
	27. Strike match		
F.	*Wheelchair Activities*		
	1. Bed to wheelchair		
	2. Wheelchair to bed		
	3. Raising and lowering foot rests		
	4. Propelling wheelchair forward 30 feet and stopping		
	5. Propelling wheelchair backward 30 feet and stopping		
	6. Locking and unlocking brakes on wheelchair		
	7. Opening and closing door in wheelchair and return		
	8. Wheelchair to chair		
	9. Chair to wheelchair		
	10. Wheelchair to toilet		
	11. Toilet to wheelchair		
	12. Wheelchair to tub and/or shower		
	13. Bathtub or shower to wheelchair		
	14. Wheelchair to automobile		
	15. Automobile to wheelchair		
	16. Wheelchair to floor		
	17. Floor to wheelchair		
G.	*Elevation Activities*		
	1. Bed to erect position		
	2. Erect position to bed		
	3. Wheelchair to erect position		
	4. Erect position to wheelchair		
	5. Chair to erect position		
	6. Erect position to chair		
	7. Erect position to chair at table		
	8. Chair at table to erect position		
	9. Upholstered chair and/or sofa to erect position		
	10. Erect position to upholstered chair or sofa		

PHYSICAL DEMANDS OF DAILY LIFE FROM BED TO JOB—*Continued*

		Date
G. *Elevation Activities (continued)*		
11. Erect position to toilet		
12. Toilet to erect position		
13. Down to floor		
14. Up from floor		
II. Walking Activities		
H. *Progressing Activities*		
1. Walking forward 30 feet		
3. Walking backward 30 feet		
4. Opening and closing door, erect and return		
I. *Gait* (Underarm crutches . . . Lofstrand Crutches . . . Wooden canes . . . Other support . . .)		
1. 4-point alternate		
2. Swing-to		
3. Swing-through		
4. 2-point alternate		
J. *Climbing Activities*		
1. Up 15 degree ramp, 3 feet		
2. Down 15 degree ramp, 3 feet		
3. Up 6 standard steps, one hand rail		
4. Down 6 standard steps, one hand rail		
5. Up 6 standard steps, no hand rail		
6. Down 6 standard steps, no hand rail		
7. Up and down one flight of stairs, one hand rail		
8. Up and down one flight of stairs, no hand rail		
9. Up curb		
a. 4″ curb		
b. 6″ curb		
c. 8″ curb		
10. Down curb		
a. 4″ curb		
b. 6″ curb		
c. 8″ curb		
11. Up bus steps		
12. Down bus steps		
K. *Travelling Activities*		
1. Cross standard street on green light		
2. Get in bus, place coin in turnstile		
3. Go through turnstile and stand holding on overhead strap		
4. Sit down and get up from bus seat		
5. Travel to middle door of bus		
6. Descend from bus to street		
7. Walk to taxi, 10 feet, open door and enter cab		
8. Descend from taxi, close door and walk 10 feet		
9. Walk forward 300 feet with package		
10. Carry cafeteria tray with dishes		

Summary:

Examiner

than the leg on the paralyzed side, and the function returns much later, if at all. If the patient is able to raise the affected leg an inch or two off the sheets while in a supine position, there is usually sufficient muscle power remaining to permit him to ambulate.

Rehabilitation for the feasible hemiplegic patient should be instituted early in the course of his illness. It has been the experience at the New York University-Bellevue Medical Center that there will be no untoward results if the patient whose apoplexy has been caused by thrombosis starts on bed activities 24 hours after regaining consciousness. In those cases where hemorrhage has been the cause, the patient is kept on bed activities alone for the first three weeks, and then is allowed to sit up in bed and to start other simple active training procedures. The embolic patients can start a full training program if there is no systemic contraindication.

We find that approximately 50 per cent of our hemiplegic patients need short leg braces to correct the toe drop so frequently seen in this disability. The double-bar, short leg brace with a 90 degree stop is used with the majority of patients. In less severe cases, the patient can be fitted with a spring-type brace, which extends from the heel of the shoe up the posterior of the leg to the calf. For cosmetic reasons, this brace is preferred by many patients.

A right hemiplegia in a right-handed person is a serious disability, because of the sensory and motor aphasia and the lack of skill in the left hand to perform the activities essential for daily living. The training of the left hand should be started early, as the patient must become left-handed if he hopes to care for his daily needs. Simple tasks in eating and dressing should be started. Left-handed writing must be practiced, as this is an important means of communication, especially when speech is affected.

It is extremely important, in cases of aphasia, for the physician to explain both to the patient and to his family the nature of aphasia and his inability to speak. This should be done as soon as the patient has recovered consciousness and aphasia is noted, in order that his fear of "losing his mind" may be allayed.

Obviously, the physician himself cannot undertake the actual administration of the retraining, but a therapist, nurse, volunteer or even a member of the family can conduct the activities under the physician's supervision. With such a program, many of the complications usually following apoplexy can be avoided and a great deal of time and ability salvaged.

Paraplegia

The paraplegic is usually considered to be a problem for the orthopedist, the neurosurgeon and the neurologist. However, in the light of our present knowledge of nutrition, the internist plays an important rôle and should be in on the management of the paraplegic at a very early date. Munro, Mulhol-

land, Co Tui and others have shown that protein metabolism plays a vital rôle in the prevention and healing of decubitus ulcers. It has been observed that a hypoproteinemia often develops within the first two or three days after the accident, with an inverse albumin-globulin ratio, and that with the hypoproteinemia comes a marked tendency to develop decubiti, even with the most meticulous nursing care. After their development, adequate healing is not possible until the hypoproteinemia is corrected. Every effort must be made, from the day of the accident, to maintain a high protein intake by every means available, the most valuable one being adequate dietary protein. This, however, can be supplemented by protein hydrolysates, whole blood and blood fractions.

Co Tui has observed, however, that in some individuals with protein depletion, in spite of a very high protein intake, it is impossible to bring blood proteins up to normal unless a program of bed exercises is inaugurated.

It is well recognized, following the studies of Keys, Barr, Dietrich, Shorr and others, that supplementary vitamin feeding is indicated to compensate for the loss that comes with bed rest.

Many problems concerning the etiology and management of decubiti are crying for solution. A striking example is the observation that individuals in their late teens and early twenties are much more prone to develop decubiti than are the older patients. It seems that an approach to the problem from an endocrine standpoint might cast revealing light on this subject.

The other common problems relating to internal medicine and rehabilitation are obviously those of the arthritic, the tuberculous, the cardiac and the neurologic patient, to name a few of the larger groups. To attack the problem adequately, there must be interest and understanding. The patients ordinarily seen in a rehabilitation program are the "crocks." (A "crock," by John Romano's definition, is "a patient from whom the diagnostic sheen has been worn.") These are the patients in the back beds of the wards and the back bedrooms of their homes. They are not particularly interesting from a teaching standpoint. There are "too many of them." Too, the doctor has a rather frustrating experience in seeing them day after day without any definite, planned program to offer.

In rehabilitation, we must teach not only the tangibles but the intangibles —not by text, but by example. In the first lecture to the freshman class at New York University College of Medicine this year, I made this statement, which I deeply believe: "If you come out of your four years in this Department with but one thing, I shall feel your time has been well spent. That one thing is this: If you can get the same deep, inner satisfaction from teaching an old, battered hemiplegic, who has been relegated to a life in bed and wheelchair, to walk again and to take care of his daily needs, that you now get from making the diagnosis of aleukemic leukemia, histoplasmosis, or some other obscure condition, then your time will have been well spent, for 75 per cent of your patients will be individuals suffering from chronic

disease, disability or related problems. If you cannot get this satisfaction from providing them with a life of dignity and at least some degree of self-sufficiency, much of your time in practice, instead of being stimulating to you, will be boring, and under these circumstances you cannot practice 'good medicine.' "

Rehabilitation should offer a "service" to the medical specialists, a service that should aid in the solution of our medically-created, Number One problem—chronic disease and disability in an aging population.

INTRACTABLE HEART FAILURE*

By Samuel Proger, M.D., and Joseph J. O'Connor, M.D.,
Boston, Massachusetts

Intractable heart failure in this discussion is defined as that failure which is apparently resistant to further treatment. An evaluation of such refractory failure should concern itself with the following questions:

1. Is the diagnosis correct?
2. Has the treatment been really adequate?
3. Has the patient been incorrectly treated and is the lack of further therapeutic response due to certain derangements resulting from this incorrect treatment?
4. If standard measures have been correctly employed, to what extent is the continuing intractability due to extracardiac factors?
5. If all possible therapy is no longer effective, what are the characteristics of the terminal stage of heart failure? These phases of the problem will be separately discussed.

Patients are occasionally considered to be no longer responsive to treatment for heart failure when this lack of response to standard measures may be due to unrecognized conditions, some of which are treatable and hence need particularly to be recognized. I refer to such conditions as thyroid heart disease, beriberi heart disease, constrictive pericarditis, and arteriovenous aneurysm, as well as to such complicating factors as anemia, hypoproteinemia, and infection. These conditions need generally only to be considered to be diagnosed.

In addition to these specifically treatable conditions which may produce an apparently intractable state, there is tricuspid stenosis. In such a situation, however, there is no heart failure in the sense of a failing ventricular muscle; hence the intractable failure in this condition is more apparent than real.

Finally, there are other differential diagnostic problems involving noncardiac disturbances which need to be considered, such as are presented, for example, by chronic glomerulonephritis and multiple pulmonary infarcts. There are thus three types of diagnostic errors which must be avoided in a consideration of intractable failure, namely, (1) that related to removable causes for such apparent failure, (2) that related to heart disease with apparent though not real failure, and (3) that related to noncardiac disease which may be confused with heart failure.

Having clarified the diagnosis, one must then be certain that the standard

* Presented at the Thirty-first Annual Session of the American College of Physicians, Boston, Mass., April 20, 1950.

From the Pratt Diagnostic Clinic, New England Center Hospital, and the Department of Medicine, Tufts College Medical School.

therapeutic measures have been applied adequately. Is the digitalis dosage sufficient? Is the salt intake maximally restricted? Have the full benefits been derived from the diuretics? Have the limitations of physical activity really been adequate? These are obvious questions and are generally easily answered once they have been asked.

There are at least two conditions in which therapeutic factors may be responsible for apparent unresponsiveness in patients with congestive heart failure of the usual type. One is the so-called low salt or salt depletion syndrome, the other is mercury fastness; the two may be closely related. Probably the commonest cause for the salt depletion syndrome is excessive mercurial diuresis. While the mercurial diuretic may be wholly excreted in 24 hours and hence may safely be given every day so far as the mercury is concerned, the effects of such a diuretic on fluid and electrolyte changes may be cumulative, persistent, and quite serious. Such harmful results may come about either because the diuresis has been apparently too successful (the salt depletion syndrome), or because the mercurial has been apparently ineffective (mercury fastness). In either case the diuretic may produce an electrolyte climate which is intolerable to life.

Any term which may be used to characterize the syndrome associated with salt depletion is likely to be misleading if it does not distinguish between the sodium and chloride factors. Because chlorides are so much more easily measurable, sodium data have in the past been frequently inferred from chloride determinations. Such inferences, unjustifiable and misleading, have carried over even into current literature. The chloride and sodium ions are both important. It is now becoming clear that while the sodium ion is of paramount importance in a consideration of problems of fluid balance, the chloride ion has its own importance as well, so that the two ions must be independently determined and separately evaluated. Thus a chloride depletion syndrome may have a different significance from a sodium depletion syndrome. There is good experimental evidence to indicate that the depletion resulting from excessive mercurial diuresis is often a chloride depletion and not a salt depletion, if by salt is meant sodium chloride. Crawford and McIntosh [1] and Blumgart, Gilligan, and Volk [2] had previously recognized the fact that mercurial diuretics would produce chloride deficit but it remained for Schwartz and Wallace [3] to point out the practical significance of this finding in relation to the problem of mercury fastness as well as some of the broader implications of electrolyte disturbances during diuresis in heart failure. Schwartz [4] was the first to show that simple chloride-depletion alkalosis has been confused with true salt depletion characterized by hyponatremia and acidosis. But it appears that one may have to go even further in specific terminology, because more than sodium and chloride are involved in the disturbances under consideration. For, in addition to hyponatremia and hypochloremia, there may be, among others, alone or in combination, such conditions as acidosis,

alkalosis, hyperkalemia, hypokalemia and azotemia. The combinations are likely to be variable, and it may be that we shall come to recognize more and more associated chemical disturbances in what in the past have been considered cardiac derangements. Following are some examples.

TABLE I

	Sodium	Chloride	CO_2	Potassium	NPN
	milliequivalents per liter				mg. %
Normal	137–143	97–105	22–30	4.0–5.0	25–40
Patient R. G.	140	83	40	4.2	45
Patient J. S.	128	93	21	4.9	58

Table 1 shows the variability of the sodium and chloride ions in patients who may have been subjected to excessive diuresis. These two patients may both be said to be suffering from the "salt depletion syndrome." In the first case only the chloride is low; in the other, the sodium and chloride values are both low. In the first case there would be no logical basis for giving salt solution, hypertonic or otherwise. The alkalosis and hypochloremia can be readily corrected by ammonium chloride. In the second case there is an apparent indication for hypertonic salt solution, although to establish an absolute indication for the hypertonic salt one would have to prove that there was no migration of sodium into the cells or dilution by water.

Table 2 shows some changes which occurred with frightening rapidity in a 69-year-old woman with arteriosclerotic heart disease and apparently intractable heart failure. She had been given 2 c.c. of mercuhydrin daily for seven days before the first recorded values and for the ensuing three days. She had had no mercurials for four days prior to the second set of values. Throughout she had been taking 6 gm. of ammonium chloride daily in enteric coated tablets. Whether this ammonium chloride was being absorbed we do not know. She was taking a low salt diet and was fully digitalized. Her daily urine output in the period recorded was only about 500 c.c., and her fluid intake about 2,000 c.c. The changes between the eighth and the fifteenth hospital day are shown. She died on the sixteenth hospital day. The chemical changes were striking; there were no correspondingly impressive clinical changes. It is impossible at this time to know to what extent the terminal changes resulted inevitably from the chain of disturbances set in motion by the initial hypochloremia. This hypochloremia may in turn have been due to excessive mercurial diuresis.

Because of the possible therapeutic implications, it is important to know that such a quiet and mysterious dissolution of vital protective mechanisms

can occur in the late stages of heart failure. One can only speculate as to the origin and nature of such a derangement.

It is expected that chemical patterns will in time emerge which will lend themselves to logical and simple therapeutic attack. This may mean that determinations of blood sodium, chloride, nonprotein nitrogen, carbon dioxide, and potassium, among others, may come to be essential to the intelligent management of a patient with advanced and stubborn heart failure. A flame photometer may become an important part of a cardiologist's diagnostic equipment.

Thus far we have considered electrolyte disturbances as possibly resulting from the inept use of diuretics and salt restriction. Is it possible that a distortion of the electrolyte partition can result from the effects of late heart failure quite independently of overaggressive therapeutic management?

The present state of concern over electrolytes in heart failure is almost wholly related to severe salt restriction and the excessive use of diuretics. Thus, serum electrolytes are rarely measured except in situations where it

TABLE II

	Sodium	Chloride	CO_2	Potassium	NPN
	milliequivalents per liter				mg. %
Normal	137–143	97–105	22–30	4.0–5.0	25–40
Patient H. M. Hospital Day 8	138	86	31.8	4.4	52
Hospital Day 15	123	78	19.5	6.4	165

is thought there might be salt depletion from overtreatment. If the blood sodium or chloride is found to be low under these circumstances, it is assumed that this deviation must be the result of overtreatment. Perhaps as blood electrolytes come to be more frequently measured, whether or not one suspects overtreatment, disturbances may come to light related to unknown and hitherto unsuspected factors in what is now regarded as the terminal stage of chronic heart failure. We have in fact noted significant deviations in electrolyte partition in the terminal stages of congestive failure which could not reasonably be attributed to excessive mercurial diuresis. Table 3 shows one such case. The patient, a male 55 years of age, had advanced arteriosclerotic heart disease. He had had two previous hospital admissions for congestive heart failure, the second one having been three months before the final admission. His failure had been well under control with digitalis, greatly restricted physical activity, and a low salt diet. He was comparatively well until two weeks prior to the third and last admission, when he developed symptoms of congestive heart failure increasing to the time of admission. He had stopped taking digitalis two days before admis-

sion. He was orthopneic, had distended neck veins, pulmonary râles, presystolic apical gallop, and an enlarged liver. The heart rate was 120 per minute. He was given 1.0 c.c. mercuhydrin intramuscularly (with negligible diuresis) and 0.4 mg. of digitoxin on the day of admission. The data in the table were obtained from blood collected the following morning.

The question naturally arises as to whether such drastic disturbances may not be simply a reflection of the dying state, whether that dying state be due to heart failure or to some other chronic condition such as widespread carcinomatosis. We have seen similar abnormal electrolyte patterns, for example, in the late stages of extensive carcinomatosis. In the presence of such carcinomatosis, a correction of the chemical disequilibrium would be of no real value. However, in congestive heart failure the restoration of equilibrium might conceivably result in a useful prolongation of life, since it is the chemical changes secondary to the heart failure which appear to constitute the immediate cause of death rather than the heart failure itself. Incidentally, there are times when similar considerations deserve attention in certain phases of the aftermath of myocardial infarction as well.

TABLE III

	Sodium	Chloride	CO_2	Potassium	NPN
	milliequivalents per liter				mg. %
Normal	137–143	97–105	22–30	4.0–5.0	25–40
Patient C. R.	126	88	23	5.6	79

Such is the evolving picture of chemical disturbances in heart failure, particularly as this failure reaches an apparently intractable phase. This phase of heart failure represents currently an area for therapeutic exploration. This area will be pierced and exploited as we attain a clearer view of the biochemical problems involved.

In the extracardiac troubles of the failing heart there is at present a tendency to lay great stress on the sodium factor. Momentum is gathering behind the potassium factor. There are those whose attention is focused on the chloride ion. There are some who are concerned about the intracellular changes; there are others who believe that organs such as the kidneys, the liver, the pituitary or the adrenals have been insufficiently incriminated.

Of the various noncardiac organs, the kidney has in the past few years been the subject of particular attention in heart failure. It has indeed been assigned a central rôle by some in the drama of the failing heart. That it deserves such a starring rôle is perhaps open to some question. It has been tempting to focus attention on the heart-kidney relationship to the exclusion of other possible important factors, as it is always tempting to take the easy

intellectual path. It is difficult to believe that the heart-kidney connection is more than one strand of many that go to make up the intricate pattern which is woven by the dilapidated heart. Much can happen and probably does in that gulf between the heart and kidneys. There has perhaps been a tendency to oversimplify the relationship between these two organs. What one finds in the kidneys may be only indirectly and remotely the result of what happens in the heart. There are many possible intermediate factors of importance. But reciprocal relationships do exist, even between distantly separated organs, and this is probably true of the heart and kidneys as well. The kidneys are of undoubted importance in the obstinate heart failure which is the subject of this discussion. Indeed there are patients, probably not insignificant in number, who are ostensibly dying of unmanageable heart failure who may be given the final push by reversible renal failure, this renal failure apparently in some patients being in turn due to the effects of treatment for the heart condition.

A sharp drop in circulating blood volume, such as is seen in shock, is capable of producing serious renal functional impairment.[5] If such an event is possible in the presence of the considerable functional reserve of the normal kidneys, it is not too much to assume that minor degrees of rapid drop in circulating blood volume might result in a similar disruption of kidney function when the renal reserve is limited, as it must be in many elderly patients who have heart failure. In these patients the heart is obviously in failure; the kidneys only have a lessened reserve. The nitrogen retention seen following the vomiting of digitalis intoxication or the dehydration of excessive diuresis may simply represent the effects on kidneys with inadequate functional reserve of a sharp drop in circulating blood volume, and hence renal blood flow.

A rapid decrease in circulating blood volume is highly desirable in patients with congestive failure. Much of our cardiac therapy is directed toward this end. Such a decrease in circulating blood volume may, however, lead to a decrease in renal blood flow and hence an impairment of renal function. Since elderly patients who are in congestive failure may already have diminished kidney reserve, and since the congestive failure itself results in diminished renal blood flow, the addition of a third hampering factor on kidney function, such as repeated sharp drops in circulating blood volume, may prove of critical importance in reducing the renal blood flow to a point where irreversible kidney insufficiency results.

The combination of the prerenal plus the renal factors may produce a picture of serious renal insufficiency where either factor alone would not be harmful. Sufficient regard is generally not given to the prerenal factors as additive rather than the sole causes of pronounced renal insufficiency. Since only these prerenal factors are correctable, it is especially important that we bear them in mind and evaluate them fully as constituting a fruitful area of therapeutic attack. It is indeed this area which is often falsely viewed as intractable heart failure.

Among the extracardiac causes for apparently intractable heart failure therefore, are peripheral chemical disturbances which may or may not involve the kidneys and which are probably correctable with a proper knowledge of the blood carbon dioxide, sodium, chloride, potassium, and nonprotein nitrogen. But the patient whose heart failure is uncontrollable may have been correctly diagnosed and his recognizable chemical disturbances properly reversed. He is still unresponsive. What then? It would appear that there must be a terminal stage of congestive failure, although it is by no means certain that a patient need inevitably die of such a failing heart. It is at least conceivable that, in time, congestive heart failure can be sufficiently reversed and brought into hemodynamic equilibrium so that it can be kept under control indefinitely. But that time is not yet. The next stage of attack on that shrinking area represented by terminal heart failure will require a clearer picture than is now available of what is meant by terminal heart failure. The exact mechanism of death in heart failure is often obscure. There are, to be sure, some recognizable causes, such as extensive pulmonary infarction, terminal bronchopneumonia, or cerebral infarcts. It is conceivable that embolization from mural thrombi may largely be controlled by anticoagulant therapy. There should certainly be fewer deaths from bronchopneumonia in this day of antibiotics. We are not here concerned with these, nor with death from conduction disturbances often seen in patients with coronary artery disease. Rather, we are concerned with the death which slowly and relentlessly comes to those patients with chronic congestive heart failure for whom all therapeutic efforts have been exhausted. If the congestive phenomena are controlled, and if the electrolyte partition is suitably maintained, we shall have pushed back the frontiers of death in congestive heart failure to a point where we shall come face to face with entirely new therapeutic problems.

The history of the management of heart failure has been one of gradually extending the range of effective therapy and of simultaneously diminishing the area of intractability. This area of intractability, while it has shrunk considerably as a result of digitalis, diuretics, etc., is still a large target. Perhaps this target can be attacked more successfully if it is more clearly defined. It has been the purpose of this discussion to indicate some of the problems involved in attempting thus to define intractable heart failure, and to indicate further some of the immediate areas of attack.

Summary

1. There are three types of diagnostic errors which must be avoided in a consideration of intractable heart failure: (1) that related to removable causes for such apparent failure, (2) that related to heart disease with apparent though not real failure, and (3) that related to noncardiac disease which may be confused with heart failure.

2. It is important to evaluate the adequacy and correctness of each phase of therapy.

3. Mercurial diuresis may result in hypochloremia with normal blood sodium and alkalosis, thus constituting one phase of the "salt depletion syndrome." This pattern may also be associated with mercury fastness.

4. A lowering of the sodium in the blood may follow an initial chloride depletion and present another and more serious aspect of the low salt syndrome.

5. It appears that a lowering of the sodium and chloride ions may occur quite independently of the excessive use of diuretics. It may in fact be a nonspecific manifestation of the dying state. In addition to hyponatremia and hypochloremia, there may be, among others, alone or in combination, such conditions as acidosis, alkalosis, hyperkalemia, hypokalemia, and azotemia.

6. It is important to recognize the prerenal factors which serve as additive causes of the pronounced renal insufficiency often seen in intractable heart failure because these factors are reversible.

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A STUDY OF THE MOVEMENTS OF HEART VALVES AND OF HEART SOUNDS * †

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For years there have been many theories and explanations given for the causes of the heart sounds. There is still considerable variance of opinion, controversy and debate among investigators as to the exact causes of the heart sounds. This is especially true of the first heart sound. It is fairly well agreed among most investigators that the second heart sound is due chiefly to the closure of the semilunar valves. Most of the controversy has been and still is concerned with the cause of the first heart sound. In the past there have been as many as 40 theories proposed to explain the first heart sound. Many of these were entirely without clinical or experimental basis. During the past few years the suggested causes of the first heart sound have been reduced to a few: (1) a valvular component, (2) a muscular component, and (3) other questionable components.

One group of investigators believes the first heart sound results chiefly, if not entirely, from closure of the auriculoventricular valves. Another group believes that the first heart sound is due not only to closure of the auriculoventricular valves but also to muscular contraction and ejection of blood from the ventricles. To our knowledge, there has not been recorded an accurate, detailed description of the exact movements of the valves, nor has there been presented a satisfactory visualization of the exact movements of the heart valves.

Our experiments were undertaken to obtain (1) more information about the detailed movements of the heart valves, and (2) more nearly accurate information about the causes of the heart sounds. The factors that are believed to cause the second heart sound are not considered in this report. It was believed that if the detailed movements of the valves of the beating mammalian heart could actually be seen and the sounds heard at the same time, it would make possible a better understanding of the origin of the first heart sound. With this in mind, the hearts of various laboratory animals were perfused with oxygenated Ringer-Locke's solution and were kept beating for various lengths of time. Rather large openings were made in the walls of the auricles. These afforded an excellent view of the movements of the entire valves. Colored motion pictures were made of the exact move-

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ments of the mitral, tricuspid, aortic and pulmonic valves, in both normal speed and slow motion. A sound recording, a visual record of the sound and an electrocardiogram were made at the same time that the motion pictures were taken. These records enable one to visualize the exact movements of the heart valves, to hear the first sound and to see simultaneously an electrical record of the sounds and an electrocardiogram.

The heart sounds were picked up by a cardiophone placed in contact with the heart itself, except for two insulating layers of a rubber membrane which were interposed. The minute electric current in the microphone was preamplified through two stages before being coupled to the sound-on-film amplifier. One stage of preamplification was necessary for coupling with the Grass power amplifier and the Brush inkwriter which was used to record the heart sounds.

Following the first stage of preamplification was a filter especially designed to pass frequencies of up to 50 cycles per second. Higher frequencies were suppressed in order to eliminate rubbing artefacts. An electrocardiogram was recorded by means of a conventional Grass preamplifier, with a power amplifier leading to a Brush recorder.

The motion picture film was made with the use of two cameras synchronized with the sound on the film. One camera recorded the movements of the heart valves and the other recorded the two ink-writing pens of the Brush recorder, the upper tracing being that of the sound and the lower tracing being that of the electrocardiogram.

It has been believed for years that increased pressure in the auricles is an important factor, if not the sole cause of the opening of the auriculoventricular valves. We were very much interested and surprised to note that the auriculoventricular valves would open vigorously in the perfused hearts when the pressure in the auricles was the same as atmospheric pressure and was not greater than the pressure in the ventricles. Determinations of pressure were made with a strain gage manometer in the two auricular cavities, in the right and left ventricular cavities, in the intact heart and in the perfused heart. The pressure in the atria when large openings had been cut in their walls was the same as the atmospheric pressure. The pressure in the right ventricle ranged from 0.83 to 2.5 mm. of mercury. The pressure in the left ventricle ranged from 8 to 72 mm. of mercury. At no time was the pressure recorded in the auricular cavities in the perfused heart greater than the pressure in the ventricles. At no time did we record any negative pressure in the ventricles. We did observe, however, that the auriculoventricular valves did not close when there was little or no fluid in the ventricles. The auriculoventricular valves would close when there was sufficient fluid in the ventricles, that is, when there was sufficient fluid between the cusps and the walls of the ventricles. The valves would close as a result of the walls' contracting upon this fluid, which forced the leaflets upward and together. When a catheter was inserted through the mitral ring into

the left ventricular cavity and the fluid was withdrawn, the valves would no longer close. When fluid in sufficient quantities was replaced in the left ventricle, the mitral valve would immediately close vigorously.

It was noted that there was a very definite sphincter-like action of the mitral and tricuspid rings. The opening of the mitral and tricuspid rings is much smaller during systole than it is in diastole. The sphincter-like contraction was rather strikingly demonstrated by cutting the mitral and tricuspid rings, laying them in a longitudinal line and noting the definite lengthening and shortening of the strip of tissue with each contraction.

While the heart was beating forcefully and was still on the sound track, the cusps of the mitral valves were excised. Then the first heart sound was heard less distinctly. Next, the cusps of the tricuspid valves were excised and the first heart sound was barely audible. We believe that this is further evidence that the first heart sound is due largely to the valvular component, that is, the valves' suddenly becoming taut and striking forcefully against each other. We believe that the forceful striking of the edges of the valves against each other produces a much louder sound than does the sudden tautening of the valves, and that such forceful striking probably is the main factor in producing the first heart sound.

DIGITALIS DELIRIUM *

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IT is hardly necessary to point out the highly practical desirability of understanding as much of the action of digitalis as possible. This drug, of course, is in exceedingly wide use and is loved by many of us "not wisely but too well." It is, as has been pointed out, "not an indifferent drug." [1]

Such effects as anorexia, nausea, vomiting, electrocardiographic changes, slowing of the pulse, bigeminal or trigeminal rhythm, diuresis, color hallucination, amblyopia and scotoma are generally recognized. Occasionally, patients receiving digitalis develop delirium. This is generally, I believe, put down as "cardiac" delirium. However, there has been a school of thought, kept alive by an occasional report since the early communication by Duroziez in 1874, that such a complication may be due to digitalis intoxication. The practical question in such cases is: does the patient deserve a rest from digitalis, or does he require continuance or augmentation of the dose of the drug to improve his condition? Correct appraisal of the dilemma and prompt action upon the proper deduction may mean life or death to the patient.

Contributions on this question are far from numerous. Much the most extensive is that of Duroziez,[1] who reported 20 cases of what he considered unfortunate or catastrophic results of digitalis therapy, including 13 instances of delirium and several deaths. Materials used in these cases included a tincture, an infusion, a powdered or macerated leaf, digitalin, and the "wine of Trousseau." Contrary to modern practice, the French physicians of that day used digitalis in cases of acute nephritis, rheumatic fever, hepatic cirrhosis and delirium tremens, as well as in cardiac disease. The report of Duroziez deserves especial consideration for this reason: a delirium appearing during digitalis therapy of cirrhosis, nephritis or, possibly, rheumatic fever, cannot easily be dismissed as of "cardiac" type. Duroziez pointed out that it was of interest to note that cases of rheumatic fever treated with digitalis were prone to pass into the "cerebral" type. He traces a case in which a patient recovered from delirium tremens, only to be overtaken by a digitalis delirium. He reports three cases of cirrhosis, with questionable cardiac complications in only one, in which use of digitalis was followed by delirium and death. Necropsy verified the diagnosis of cirrhosis in each case. Among cardiac cases, he had the impression that patients with aortic valve lesions or anemia might not tolerate digitalis so well as others. He concludes that the drug should be used cautiously in anemia, aortic insufficiency, nephritis, hepatic cirrhosis, rheumatic fever and fatty degeneration of the heart. He found it well tolerated in delirium tremens, mitral insuf-

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ficiency and typhoid fever. Its use should be guarded in the elderly and probably in women and children.

Duroziez apparently recognized *pulsus bigeminus* or *trigeminus* as an indication of digitalis saturation. In some cases, the diagnosis of digitalis delirium was strengthened by withdrawal of the drug and clearing of the psyche. In other cases, this maneuver was not carried out as the possibility of delirium due to digitalis was not considered during therapy. He found it impossible to characterize accurately the delirium occurring during digitalis therapy; it seemed to vary according to the personality and intelligence of the patient and the type and severity of the illness. Pallor and some degree of tachycardia were the rule. The delirium was not necessarily fatal, but it was considered a grave sign that might eventuate in death if permitted to continue.

In a letter to Dr. Russell, of Worcester, Withering [2] wrote: "Sometimes the brain is considerably affected by the medicine (digitalis) and indistinct vision ensues." He does not mention delirium, though he believed he had cured a patient of "insanity" by digitalis therapy and induction of diuresis. Head [3] made a careful study of abnormal mental states in heart disease, reporting depression, suspiciousness and hallucination (usually a human figure), but he makes no specific mention of digitalis. Hall [4, 5] recorded three cases of hallucination thought to have resulted from digitalis therapy. Riesman [6] observed hallucination, excitation, disorientation, acute mania and delusion in cardiac patients. He considers digitalis, but wonders why delirium is not more common if it could be induced by such a widely used drug. He believed that digitalis might cause occasional delirium, but, for the general run of cases, stressed acidosis, renal insufficiency, venous stasis, cerebral sclerosis and the absorption of toxic material into the blood stream during diuresis. He mentions a case illustrating the last named theory, in which no digitalis had been administered. On the other hand, Carr [7] found delirium in a patient treated with digitalis for cardiac decompensation in which the degree of decompensation was unchanged; nevertheless, he favored disturbance of cerebral circulation rather than digitalis as the cause of the delirium. Moench [8] reported three striking cases: a woman of 61, with mitral insufficiency, developed a suicidal depression while on digitalis, was well two days after withdrawal of the drug; a Negro male, aged 39, with aortic stenosis and insufficiency, became maniacal while on the drug and required restraint, recovering in 24 hours after digitalis was discontinued; a white woman of 45, with mitral insufficiency, had similar symptoms which cleared in two days after he stopped digitalis therapy. Moench deduced that mental symptoms could be produced by even moderate dosage with digitalis.

Weiss [9] reverted to much the same views as were expressed by Riesman. He found delirium more common among the elderly and in patients with severe decompensation of the circulation. Psychosis was noted in such

cases even when no digitalis was used. He could find no correlation statistically between digitalis and psychosis, but believed psychosis to be a manifestation of disturbance of cerebral circulation: either the cerebral circulation is suddenly disturbed from the use of digitalis, or toxic products causing delirium are absorbed into the blood during withdrawal of edema fluid from the tissues.

This seems to have quieted discussion for five years; in 1937, Willius [10] swung to the theory of psychic disturbance through digitalis. Digitalis, he felt, has a potentially toxic effect on the brain; beginning with restlessness and irritability, the subject may develop disorientation as to time and place. Eventually, such disturbances may lead to stupor and even death. In the following year, Smith,[11] also of the Mayo Clinic, elaborated on the same subject. He found that patients with mental disturbances associated with digitalis therapy (headaches, depression, excitement, impaired memory, confusion, delirium, convulsions) were usually over 50 years of age and arteriosclerotic. They usually had taken digitalis a long while. Other causes of delirium were absent. The delirium was found to resemble that caused by other drugs. Similar views are expressed by Goodman and Gilman.[12] The cerebral pathology following lethal doses of digitalis administered to animals has been recorded (Hueper,[13] Hueper and Ichniowski).

So the argument has swung to and fro. In spite of considerable opinion to the contrary (v.s.), I have a distinct impression that delirium encountered during the treatment of cardiac patients, even those receiving large amounts of digitalis, is generally regarded as "cardiac delirium," requiring continued use of the drug or even an increase in dosage. Because of the dire effects that were believed by Duroziez and others to follow such a course (at least in some cases), I believe the question should be reëxamined. With this in view, I have collected the following cases from my personal experience.

Case Reports

Case 1. A Negress, aged 33, was admitted to Johns Hopkins Hospital October 8, 1947. She complained of dropsy of four weeks' duration.

The family history was unimportant. In her background, none of the "rheumatic" stigmata could be elicited. She had suffered from headaches and eye trouble for four years and had been told that these symptoms were caused by high blood pressure. She had had no nervous or mental disturbance save a certain feeling of apprehensiveness since the present illness set in.

In addition to headaches, she had noted dyspnea for more than a year, also cough, nocturia and a gain of 40 pounds in weight; most of this weight was subsequently lost by dieting. Three months before admission she had entered a local hospital, where she received digitalis. This had to be discontinued because of nausea and vomiting. Two months before admission, edema of the feet appeared, associated with oliguria. No further digitalis was given until she appeared in Baltimore.

The blood pressure was 115/95 mm. Hg. Temperature 100.2°. Pulse 90, regular. Respirations 27. She was "coöperative, fairly intelligent and reliable." The heart was enlarged to left and right. There was an apical systolic murmur, well transmitted, and a protodiastolic gallop. There was moderate edema of the legs. Tests

showed: serologic examinations negative; circulation time 23 seconds; venous pressure 108; phenolsulfonphthalein elimination in 30 minutes was 18 per cent.

A diagnosis of rheumatic myocarditis was made at admission. Subsequently, phlebothrombosis appeared in the left leg, and infarction of the lung was noted.

On admission, Lanatoside C 0.4 mg. was given, followed by 0.2 mg. every four hours for three doses. Next day, October 9, 0.1 mg. was ordered daily. Though there is some discrepancy between the notes of the nurse and house-officer, the latter noted on October 11 that the patient had received 1.6 gm. Lanatoside C and should be digitalized. (She was quite small.) However, there was no improvement in her condition. Phenolsulfonphthalein elimination on October 11 was 37.5 per cent in two hours. On this date the non-protein nitrogen of the blood was 28 mg. per 100 c.c. On the same day she vomited occasionally. Electrocardiograms were not very remarkable but showed digitalis effect on the S–T segments and, initially, predominance

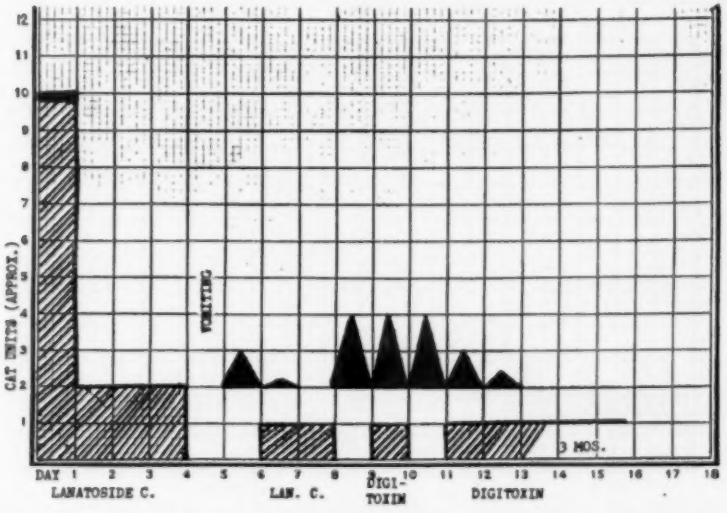

FIG. 1. *Case 1.* Delirium from Lanatoside. Improvement after interruption, reappearance of delirium (solid triangles) on resumed treatment. No clinical improvement.

of the levogram. Incident to the pulmonary infarct, there was a subsequent shift of the axis toward the right. There were probably at least two infarctions—on October 12 and on October 28 or 29.

The patient was vomiting October 12 and received no Lanatoside C. Vomiting was followed on October 13 by delirium, with disorientation. No digitalis was given October 12 and 13, and on October 14 patient was clearer mentally. To test the possible relation of Lanatoside to delirium, the drug was given in daily doses of 0.1 mg. October 14 and 15. From October 16 to 19 the patient was completely disoriented, combative, negativistic, and required the use of restraining sheets. Lanatoside was omitted October 16. Digitoxin (0.1 mg.) was given on October 17, omitted on October 18. By October 21 she was quite clear, coöperative and pleasant. Restraining sheets were removed. During the height of the delirium the blood non-protein nitrogen (October 16) had been only 32 mg. per 100 c.c.

Meanwhile, digitoxin (0.1 mg. daily) had been resumed October 19, and this was continued for about three months without complication. The dose was then 0.15 mg. daily until her discharge a month or so later.

This patient had an irregular fever October 8 to 13. After that it was essentially normal until October 29, when she had a pulmonary embolus again. It proved impossible to relate the delirium to the fever. At various times she received penicillin, ammonium chloride, aminophylline and Dicumarol.

In this case, nausea and a moderate degree of disorientation caused withdrawal of Lanatoside C for two days, with improvement of the mental status. After resumption of therapy for two days, an excited delirium appeared, lasting several days. Interrupted doses were followed by complete mental clearing. Subsequently, digitoxin, 0.1 mg. to 0.15 mg. daily, was well tolerated.

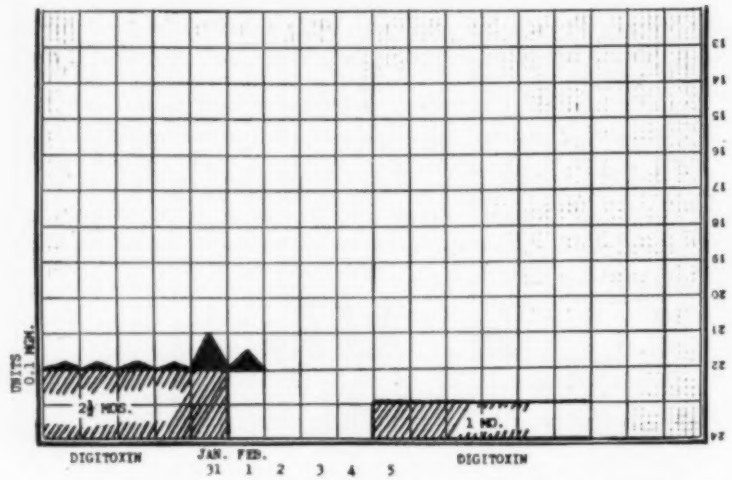

FIG. 2. *Case 2.* Delirium on full chronic dose. Prompt mental clearing on withdrawal of drug. No disturbance on smaller dose. Death.

Case 2. A white male, aged 55, married, was admitted to Johns Hopkins Hospital in the summer of 1948. He had a mild diabetes, which was controlled without insulin. There was also general anasarca, with fluid in all body cavities. He was discharged in November, 1948, weighing 130 pounds.

The patient continued to take 0.2 mg. of digitoxin daily from his discharge in November, 1948, until readmission on January 19, 1949. There was no mental disturbance during that time.

On the second admission the patient weighed 154 pounds, showed edema of legs, face, arms and trunk, and fluid in all body cavities; otherwise examination was strikingly normal. Blood pressure was 170–185/100–112 mm. Hg. Electrocardiograms showed low voltage of Q–R–S complexes and digitalis effect. Urine showed albumin, 2 gm. per liter, occasional erythrocytes, casts 3 plus on admission. Casts subsequently disappeared. Phenolsulfonphthalein elimination was less than 2 per

cent in two hours. Serologic tests for syphilis were negative. Blood non-protein nitrogen was 93 mg. January 20, 107 mg. January 31. Blood proteins were 6.3 to 6.5 gm. CO_2 of blood was 23.7 to 25.8 mEq. The condition was attributed primarily to the kidneys, which were thought to be involved probably by the Kimmelstiel-Wilson pathology, with diabetes and probably cardiac strain.

The house officer considered that this patient had been slightly disturbed mentally since admission. However, digitoxin was continued, also a salt free régime without mercurial diuretics. On January 31, the patient was found out of bed in his chair. He said he was in Pikesville, wished to telephone for transportation home. He was calm, but his attitude had been unusually stoical throughout his extreme illness, which included loss of reading vision from retinitis. On February 1 no digitoxin was given. February 2 found the patient quite clear, perfectly oriented. About February 5, digitoxin was resumed in smaller daily doses (0.1 mg.). He remained quite clear until his sudden death on March 4. There was continuous

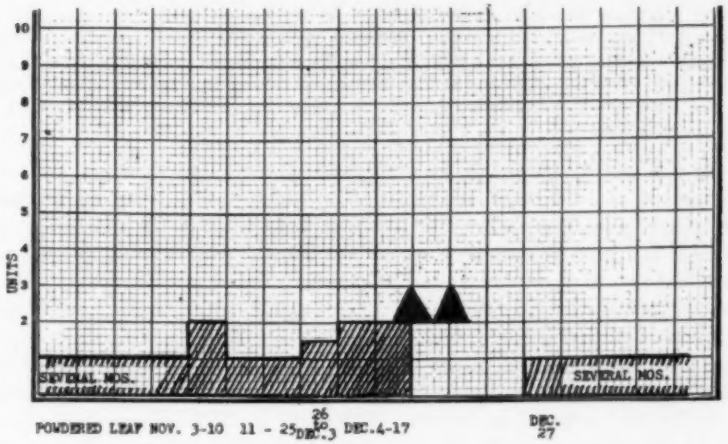

FIG. 3. *Case 3.* Delirium, agitated, after increase of chronic dose of powdered leaf. Mental clearing on withdrawal of drug. No recurrence on smaller dose.

reduction of the enormous anasarca associated with repeated tapping and salt restriction. During the earlier phase of this fluid loss the delirium appeared or became aggravated; subsequently, and after the dose of digitoxin was reduced, there was not the slightest clouding of the psyche, though loss of anasarca continued until exitus. Necropsy findings: Arteriosclerotic nephritis with intercapillary changes. Generalized arteriosclerosis, severe. Anasarca. Hypertrophy, slight, and dilatation of heart. Coronary sclerosis. Myocardial infarcts. Portal cirrhosis, early. Atrophy of pancreas, etc.

Case 3. A white, married man of 68 years was seen in The Beck private hospital in the fall and winter of 1938–1939. The blood pressure had been 204/110 mm. Hg in 1937, but a prostatectomy had been performed in November, 1937, and subsequently the pressure fell to 168/80. Dyspnea developed shortly before admission.

Examination November 11, 1938, showed enlargement of the heart (6 cm. R., 13 cm. L.). There were a mitral systolic murmur and passive congestion of the

lungs and liver. There was no cyanosis or obvious edema. Blood counts and urine were normal except for intermittent albuminuria.

For several months before admission to hospital in November, 1938, the patient had taken 0.1 gm. powdered leaf digitalis daily. In June, 1938, digitalis effect had been noted on the electrocardiogram. On November 3 the digitalis was increased to 0.1 gm. twice daily. He was admitted to hospital November 8, 1938. November 8 to 10 he received one cat unit digifolin (1 M) twice daily; November 10 to 26, powdered leaf 0.1 gm. daily. November 26 to December 4 he was given 0.1 gm. powdered leaf daily, alternating with 0.1 gm. powdered leaf twice daily. From December 4 to 17 he had 0.1 gm. powdered leaf twice each day.

By December 14 nourishment had to be given intravenously because of anorexia and delirium. The patient was disoriented, confused and required restraint. His general condition was very poor, cyanosis marked. This state continued for several days.

On December 18 digitalis was reduced to 0.1 that day; none was given December 19 to 26. During the week of withholding of digitalis the patient's appetite and mental condition improved. By December 27 he was oriented. On that date he received 0.1 gm. powdered leaf and continued to take this amount each day without trouble. He spent the summer following his illness in Maine and did fairly well until May, 1940, when he died of cerebral thrombosis and bronchopneumonia. Though he had three cerebral accidents toward the end of his life, there was no return of agitated delirium.

In this case numerous drugs were used—belladonna, laxatives, vitamins, ammonium chloride and salyrgan. The patient also received bromide, Schlesinger's solution (when delirious), and chloral hydrate. However, the bromide had been discontinued eight days before the delirium appeared, and I can find record of only two single doses of Schlesinger's, as well as a single dose of bromide 25 gr., which were given during the phase of excitement. It has been impossible to correlate the delirium of mid-December with any drug other than digitalis, which had been administered in twice the patient's usual dose for two weeks prior to December 17. The non-protein nitrogen of the blood fluctuated as follows: November 3, 1938, 57 mg.; November 25, 34 mg.; December 22, 23 mg.; January 5, 1939, 35 mg.; January 25, 62 mg.; March 6, 50 mg. Thus the non-protein nitrogen was least on the day nearest the phase of delirium.

Case 4. A white, married male, aged 73, a retired business man, was seen at Union Memorial Hospital on December 8, 1948. The complaint was shortness of breath.

In the background, none of the rheumatic stigmata nor excessive tonsillitis was reported. In 1944, the patient had had a slight cerebral accident. Since that episode, the patient had visited his office only in the mornings, leading otherwise a very quiet life. Because of certain cardiac findings, he took 0.1 gm. powdered leaf of digitalis each day during these years without untoward symptoms. There had been only a slight, intermittent elevation of blood pressure.

On the night of November 27, 1948, the patient had an attack of intense dyspnea, with pulmonary edema. Thereafter, the dose of digitalis was doubled (to 0.2 gm. each day). He was admitted to hospital November 28. He became restless and behaved in a manner so frivolous as to worry his wife—"quite unlike his usual dignified self." He could not remember the attack at the onset of his present illness on

November 27. He inquired about his trunk, was interested in getting it packed for an approaching trip, though no trip was contemplated. His wife reported that he had never had any previous mental aberration.

When seen December 8 he was found to have signs of rheumatic heart disease, with aortic stenosis and insufficiency, mitral stenosis and (probably) insufficiency. Pulse was regular, the pressure 140/84 mm. Hg. Lungs were clear. The heart was enlarged to the left. Liver was slightly ptosed, not tender. There was no edema.

It was agreed that aminophylline be substituted for digitalis, which was stopped. By December 10 the patient was much clearer and, when seen on December 11, was perfectly normal mentally. He died January 6, 1950. There was no subsequent mental disturbance whatever.

Case 5. A clergyman was first seen in 1935 at the age of 69. He had fainted during a severe sciatic pain. Twenty years before he had fainted several times.

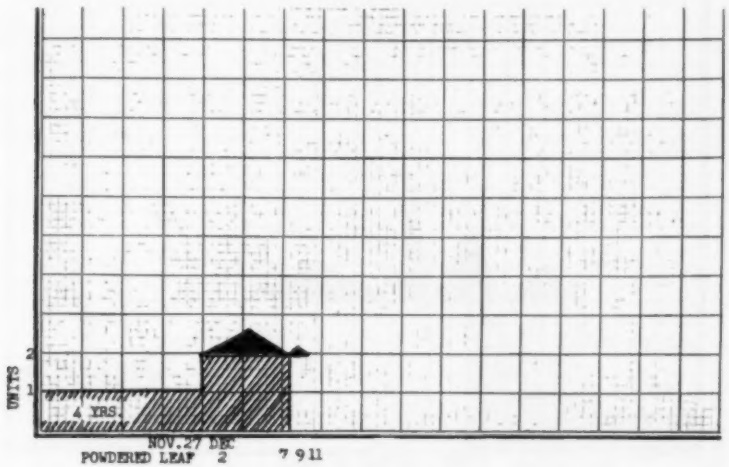

FIG. 4. *Case 4.* Delirium following increase in chronic dose of powdered leaf. Prompt mental clearing on withdrawal of drug. No change in general condition.

The background of this patient was otherwise uneventful. No significant infections were reported. The patient had a chronic scoliosis. Blood pressure was 180/104 mm. Hg. A harsh, high-pitched systolic murmur was heard both at the apex and at the aortic area. The latter was transmitted over the great vessels. No diastolic murmur was heard. The heart was not enlarged under the fluoroscope. Urine showed albumin 1 plus, was otherwise negative. Electrocardiogram (limb leads) was normal. Since 1935, my views on the significance of aortic systolic murmurs have changed, under the influence of Christian and Sosman. When the patient was seen again in his last illness, the diagnosis of calcific aortic stenosis was made.

He continued at work until shortly before his final illness in 1947. Because of attacks of pulmonary edema he was admitted to the Church Home and Hospital October 15. There were pulmonary congestion, cardiac enlargement and auricular fibrillation, in addition to the previously noted findings. Blood pressure was 210/110 mm. Hg. Serologic tests for syphilis were negative, blood non-protein nitrogen 25 mg. per 100 c.c., blood counts normal. There was albuminuria on admission but

this cleared up entirely. Roentgenogram, October 16, showed a "pneumonic process" at the right lung base. The temperature being normal, the nature of this process is obscure; it seems likely that it was a pulmonary infarct. By October 22 the lung fields had cleared considerably and there was no note of consolidation. Electrocardiogram on October 20 showed auricular fibrillation and digitalis effect.

The patient's attending physician had given him 0.1 gm. powdered leaf digitalis three times daily for 10 days before admission. He was "well oriented as to time and place" on admission. Between October 15 and 17 the patient received 0.2 mg. digitoxin orally twice each day. On October 16 he was "slightly irrational," attempting to get out of bed. October 17 and 18 he was "very irrational—difficult to sedate, tearing at oxygen tent, attempting to get up." On October 19, he was "violent and belligerent." In addition to digitalis preparations, the patient received penicillin

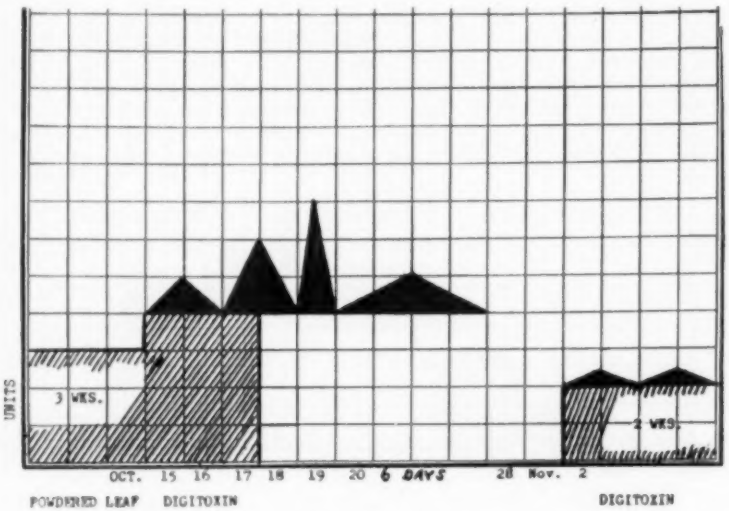

FIG. 5. *Case 5.* Combative delirium (solid triangles) following powdered leaf and digitoxin. Clearing after interruption of treatment, low delirium on resumption. No general improvement. Death.

and ammonium chloride. When the delirium became severe, he received some paraldehyde and sodium amytal.

On October 18 it was suggested that the delirium might have been induced by digitalis. The last dose of digitoxin (0.2 mg. daily) was given October 17. Thereafter no digitalis preparations were given until digitoxin, 0.2 mg. B.D. was given on November 21 and 0.2 mg. daily thereafter.

After the interruption of digitoxin therapy on October 18, the patient was very disturbed through October 19. By October 28 he "had done well during the last week," was "perfectly rational." After digitoxin was resumed at reduced dosage, his condition was noted as "slightly disoriented at times," "quite disoriented," "at times clear, at times disoriented." On November 14 he was "perfectly rational." Dyspnea persisted, edema of the legs set in, and he died November 17.

In this case, violent delirium coincided with the end of a heavy course of digitalis therapy; complete interruption of digitalis was followed by complete clearing of the psyche. Subsequent lighter digitoxin therapy was associated with mild delirium, consisting chiefly of disorientation.

Case 6. A white man, aged 62, was seen on October 8, 1937, having suffered a severe attack of retrosternal pain two days before. There was no clear history of previous "rheumatic" stigmata. All his adult life the patient had experienced sensations of sudden faintness or threatened syncope. The blood pressure was 124/70 mm. Hg. The heart was slightly enlarged to the left. There was a soft diastolic murmur along the left sternal border. Temperature was slightly elevated two days after the attack of pain. Serologic tests for syphilis were negative. Electrocardiogram subsequently indicated a healing anterior coronary occlusion. Diagnosis was:

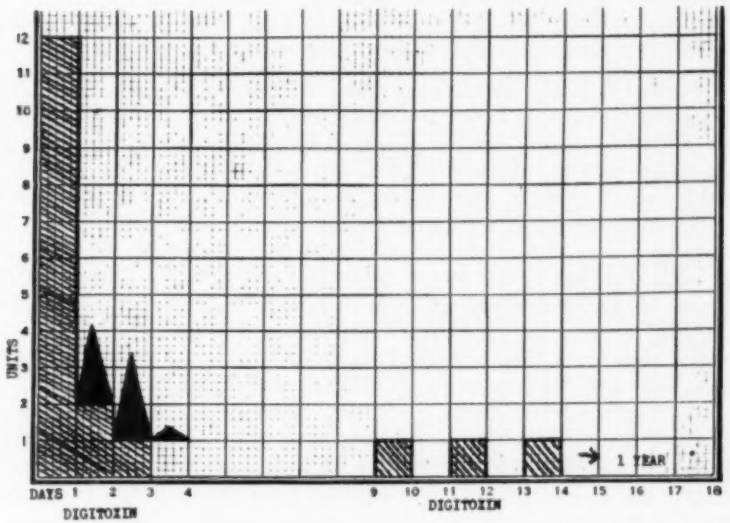

FIG. 6. *Case 6.* Sharp delirium (solid triangles) from digitoxin. No edema. No other medication. Prompt recovery.

rheumatic heart disease, aortic insufficiency, coronary occlusion.

A few months later, the blood pressure was 160/65 mm. Hg. The patient did fairly well for 10 years. On April 17, 1947, he had another attack of retrosternal pain, intermittent, requiring morphia for relief. There was slight fever on the second day. Electrocardiograms showed changes of coronary occlusion, again of the anterior type.

After recovery from this attack, the patient did not do very well, being subject to attacks of acute dyspnea, with some pulmonary edema. Dr. Louis P. Hamburger, Jr. and I decided to use digitalis. "Crystodigin" was given on the morning of July 11, the patient receiving the full calculated desideratum (1.2 mg.) by mouth. On the following morning he received 0.2 mg. by mouth. On July 13 one ampul of "Digifoline" was given. On July 12 he was restless, agitated, delirious and combative. When we arrived on July 13 the family was gathered around the bed trying to hold

the patient down. Medication was stopped, and none was given the following day. On the third morning (July 15) the patient was quite clear and rational. He continued so until his death about a year later. Subsequent administration of 0.1 mg. digitoxin every other day was well borne.

In Dr. Hamburger's notes the word "irrational" appears under date of July 10. Before the administration of digitalis July 11, he was found "somewhat confused, very depressed." However, there was no suggestion of agitated delirium until the patient became saturated with digitalis; the mental state cleared completely in less than 48 hours after interruption of the drug. In the year of life that remained to this patient, there was no further mental disturbance, nor had there been any such symptom in the 72 years that preceded his violent delirium.

Discussion

No one has denied that disorientation, delirium and other manifestations of cerebral disturbance occur in occasional cases of cardiac disease treated with digitalis. Some, notably Weiss, have emphasized the occurrence of such symptoms in cardiac patients who receive no digitalis; others, including myself, cannot recall a case of excited delirium, such as reported in the present communication, except when digitalis or some other toxic drug was being given—that is, if uremia or other recognized cause could be ruled out. Riesman and Weiss do not deny that delirium may be observed during, and perhaps because of, digitalis therapy. They simply emphasize the belief that delirium is incident to some sort of jolt or acceleration of the cerebral circulation in a sclerotic individual, or to the absorption of toxic edema fluid into the blood stream, associated with digitalis diuresis.

The hypothesis that delirium during digitalis therapy is most apt to occur in elderly or arteriosclerotic individuals is a reasonable and tempting one, and is mentioned in many of the above reports. However, I cannot find that the ages of patients with delirium have been compared with those of any large group of other cardiac patients. Among recorded cases of supposed digitalis delirium, patients' ages have been noted as follows:

Author	Male	Female	Unspecified
Duroziez	65, 50, 70, 48, 40, 63, 36	74	72, 71
Carr	54 ("Elderly")		
Moench	39	61, 45	
Author	55, 68, 73, 81, 72	33	

It would be hazardous to draw an immediate conclusion that arteriosclerosis of the brain was a necessary or very unusual attribute of such a group of patients, or that the recorded ages are much out of line with those of cardiac cases in general. During the 75 years covered by these reports, heart disease has shown a numerical increase, both relative and absolute, in

the upper decades of life. In the years 1920 to 1940 the degenerative cardiopathies constituted quite a variable percentage in the reported morbidity rates,[15] making it impossible to discover the average ages of the various cardiac types. Moreover, though my last four patients were all elderly, three had an aortic valve lesion that, strictly speaking, was probably of the rheumatic type. In the cases alluded to in the above analysis, the ages of 12 (66 2/3 per cent) were 50 or more, while six (33 1/3 per cent) were less than 50 years of age. I have not been able to find a basis for the suggestion by Duroziez that women and children, as well as elderly individuals, might be sensitive to the cerebral effects of digitalis. Thus it may be said that, while cerebral sclerosis or disturbance of the cerebral circulation cannot be said *not* to play a rôle in the induction of digitalis delirium, the importance of such factors per se has not been established. Finally, if Duroziez is correct, digitalis delirium may occur in the absence of important circulatory disease, as noted in his three cases of hepatic cirrhosis treated with the drug.

Another attractive suggestion has been that delirium developing during digitalis therapy is due to an effect upon the brain of certain toxic substances that enter the blood from edema fluid during diuresis. This is even more difficult to establish. As I read the Duroziez report, edema was noted in six cases, resulting from heart disease in five and from hepatic cirrhosis in one. Edema was reported as unchanged during treatment in one case, as diminished in one or possibly two cases, and as increased in one case. In the remaining two cases the course of edema is difficult to follow. In a case reported by Hall, the degree of cardiac decompensation remained unchanged by digitalis. Among my patients, a note was made in case 1 shortly before delirium set in that no diuresis had occurred and that the patient was unimproved. In case 2, delirium appeared to be aggravated during partial reduction of enormous anasarca by repeated tapping and restriction of salt. However, delirium cleared promptly on withdrawal of digitalis. It did not recur to the slightest degree, although reduction of anasarca continued for four weeks and digitalis was reintroduced, after a four day intermission, at half the original dose. In none of my last four cases was any apparent edema noted. Thus, the possible relation of delirium to the absorption of edema fluid remains, at best, a highly speculative hypothesis.

After assembling the above cases, I have encountered a report read by Andrus and Padget before the American Clinical and Climatological Association in 1933. These observers found 440 cases of myocardial insufficiency among 2,244 patients admitted to Baltimore City Hospitals. Only seven of the 440 were found to have a major form of delirium. Only four of their seven cases are reported in detail. Among these, digitalis might have been responsible for the delirium in one, but it is impossible to incriminate this drug in the other three. In discussion, Pincoffs related a case observed by himself in which delirium cleared promptly on discontinuing digitalis therapy. While I have not encountered a case of agitated

delirium except in patients receiving digitalis, it seems clear that such incidents can occur.

Conclusions

1. Six cases are reported in which delirium occurred in association with digitalis therapy. In each case, the disturbance cleared entirely on withdrawal of the drug or reduction in its dosage.

2. Deficiency in cerebral circulation may play a predisposing rôle, but it is hazardous to place too much emphasis on arteriosclerosis or age. Three of the cases reported had aortic valve lesions, probably on a rheumatic basis.

3. The delirium seems to be due to drug intoxication, rather than to changes in circulation or absorption of edema products, in these cases.

4. Causative preparations included powdered leaf of digitalis, Lanatoside C and digitoxin.

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SPONTANEOUS PNEUMOTHORAX—CONTRAST OF THE BENIGN IDIOPATHIC AND THE TUBERCULOUS TYPES *

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SPONTANEOUS pneumothorax has been known to physicians for many years. The dramatic picture of sudden unilateral chest pain with dyspnea and the finding of a collapsed lung on physical examination and chest roentgenogram are easily recognized. Since spontaneous pneumothorax may occur in patients with pulmonary tuberculosis, it was commonly believed that all spontaneous pneumothoraces were tuberculous. Kjaergaard [1] in 1932 published an excellent monograph describing his studies of 51 cases of spontaneous pneumothorax in apparently healthy people without any evidence of pulmonary tuberculosis. Other studies [2, 3, 4, 5, 6, 7, 8, 9, 10] soon revealed that spontaneous pneumothorax could be produced by diseases other than tuberculosis, for example, bacterial pneumonia,[3] and could occur in healthy individuals without any apparent lung disease. It became important to differentiate spontaneous pneumothorax caused by tuberculosis from that occurring in the healthy, because of the great differences in treatment and prognosis. To incarcerate a patient with benign idiopathic spontaneous pneumothorax in a tuberculosis sanatorium for one or more years is unnecessary and an error.

The exact frequencies of benign idiopathic spontaneous pneumothorax and tuberculous pneumothorax are difficult to determine. The former entity is often unrecognized as such and diagnosed as tuberculous, despite the absence of any tuberculosis. Ornstein and Ulmar [9] quote Biach that, of 918 cases of spontaneous pneumothorax, 715 were caused by pulmonary tuberculosis. These figures must be accepted with caution. A physician in a tuberculosis sanatorium would be likely to see many more cases of tuberculous spontaneous pneumothorax, whereas one in general practice would see more cases of benign idiopathic spontaneous pneumothorax.

At the Birmingham Veterans Administration Hospital, the Thoracic Service (average bed capacity, 350) cares for patients with both tuberculous and nontuberculous disease. In a two year period, there have been 41 cases of benign idiopathic spontaneous pneumothorax but only 10 cases of tuberculous spontaneous pneumothorax. To contrast benign idiopathic spontaneous pneumothorax (which occurs in apparently healthy individuals) and

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tuberculous spontaneous pneumothorax (which occurs in patients with pulmonary tuberculosis), our data, based on 76 cases of the former and 35 patients with the latter, are presented.

I. Benign Spontaneous Pneumothorax [2]

Several reports have appeared in the literature recently [1, 2, 4, 5, 6, 7, 8, 9, 10] as this entity is being recognized more frequently. In 1943 the United States Army had 873 hospital admissions for benign idiopathic spontaneous pneumothorax.

The ages of the patients varied greatly. In our series, the youngest patient was 18 and the eldest was 62 years of age. Almost 50 per cent of the entire group was between 20 and 30 years.

Males are more frequently affected, in a ratio of about 5 to 1. Each side of the chest is equally involved. The time for reëxpansion of the collapsed lung varies greatly and it is difficult to predict in the individual patient. In almost 70 per cent of the patients, the time for reëxpansion of the collapsed lung was seven weeks or less. Two-thirds of the patients will require from four to eight weeks completely to reëxpand their collapsed lungs.

The etiology is unknown. The patients are apparently healthy. A very few have a history of bronchial asthma, but none in our series had had an asthmatic attack at the onset of the spontaneous pneumothorax. It has been noted by us that almost every patient has been underweight. Several patients were of normal weight, but none was obese. Spontaneous pneumothorax has no relation to effort. The history of effort associated with the onset of symptoms is apparently coincidental, and occurred in 3 per cent of our cases. Chest pain occurred in almost 100 per cent of the cases, being unnoted by one patient. Pain is usually described as "sharp" and "cutting," rarely as "dull," and was always on the side of the pneumothorax. Frequently the pain was pleuritic and lasted from one to four days. However, benign idiopathic spontaneous pneumothorax may be completely asymptomatic and may be detected on a routine chest film. Wilson [4] found five cases of asymptomatic spontaneous pneumothorax on routine chest roentgenrays of Yale students in a four-year period. Dyspnea was noted in 83 per cent of the patients in our group, and cyanosis was found in 8 per cent.

In a previous report,[2] it has been emphasized that patients with benign idiopathic spontaneous pneumothorax do not reveal lateral pleural adhesions on the chest roentgenogram. This has been true for the present series of 76 cases. Also to be emphasized is the fact that in the present group of 76 cases, only four had fluid significantly above the level of the diaphragm, and in all of these cases aspiration revealed pure bloody fluid. All other patients with benign spontaneous pneumothorax had either no fluid or fluid simply filling the costophrenic angle to the level of the diaphragm. Chest roentgenogram in the benign group reveals no pulmonary infiltration either at the time of the lung collapse or later, when the lung is reëxpanded.

Only 10 per cent of the patients in this group had fever, and this never lasted more than seven days. The white blood count and the sedimentation rate were normal in 70 per cent of the cases. Twenty per cent of the patients with benign idiopathic spontaneous pneumothorax have a recurrence.

Treatment is symptomatic. The patient is kept at bedrest until the collapsed lung has reëxpanded. Bathroom privileges are permitted when the lung has reëxpanded to about 80 or 85 per cent of its volume. Following complete reëxpansion, the patient is allowed full activity and a return to normal life. Active intervention is required only in those few cases of tension pneumothorax where aspiration of air and the institution of underwater drainage of the pleural cavity may be life saving.

II. Tuberculous Spontaneous Pneumothorax [11]

Tuberculous spontaneous pneumothorax is usually secondary to subpleural caseation with erosion and rupture of the visceral pleura. Air enters the pleural space and the lung on that side collapses. Symptoms vary from none to a sharp, acute, tearing chest pain with dyspnea. Of the group of 35 patients with tuberculous spontaneous pneumothorax, 25, or 71 per cent, had sudden pain on the affected side. Since most of these patients were fairly ill with their pulmonary tuberculosis, it is possible that their pain thresholds were elevated, and actually more would have noticed pain if they had not been so ill. Effort was not the cause of tuberculous spontaneous pneumothorax in any patient. Dyspnea was noted by 27 patients, or 77 per cent of the group.

Examination of the chest roentgen-ray revealed tuberculous infiltration of varying degree but almost always far advanced. Lateral pleural adhesions were demonstrable on the chest film in 32 patients, or 91 per cent of the group. Pleural fluid was above the level of the diaphragm in 54 per cent of these patients.

Tuberculous spontaneous pneumothorax may affect either side with equal frequency. In this series, 19 patients had a right pneumothorax, 14 patients had a left pneumothorax, and two patients had a right spontaneous pneumothorax first, to be followed later by a left spontaneous pneumothorax. Four patients had subcutaneous emphysema.

Patients who develop tuberculous spontaneous pneumothorax usually are fairly ill with their pulmonary disease. The sudden onset of a spontaneous pneumothorax, with or without pleural fluid, adds to the patient's respiratory embarrassment and toxemia. Fever and tachycardia are common, and the fever is usually prolonged.

The pleural fluid varied from serous to purulent, and often revealed acid-fast bacilli on concentrate and culture. Of this group, one-half had normal sedimentation rates and one-half had normal white blood counts with their tuberculous spontaneous pneumothorax.

The ages of the present group of 35 patients varied from 19 to 70 years.

The immediate hospital mortality rate was 29 per cent. This is caused by both the patient's pulmonary disease and his tuberculous spontaneous pneumothorax. The ultimate mortality rate is probably higher. This cannot be stated definitely, since most of these patients were transferred to other tuberculosis sanatoria for further prolonged care.

Treatment varies with the degree of symptoms. If dyspnea is not severe, no specific therapy is indicated. If a tension pneumothorax is present, an indwelling needle with under-water drainage is extremely valuable for reducing the increased intrapleural pressure. Management of the pleural effusion varies. Patients with minimal fluid require no thoracentesis. If

TABLE I

Contrast of Benign Idiopathic Spontaneous Pneumothorax, and Tuberculous Spontaneous Pneumothorax

	Benign Idiopathic Spontaneous Pneumothorax (76 cases)	Tuberculous Spontaneous Pneumothorax (35 cases)
1. Pulmonary infiltration on chest x-ray	0%	100%
2. Pleural adhesions	0%	91%
3. Pleural fluid above level of diaphragm	5% (These 4 patients had grossly bloody fluid)	54%
4. Immediate hospital mortality rate	0%	29%
5. Clinically ill	Not usually, and only very briefly (1–2 days)	Almost always
6. Fever present	If present, for only a few days, never more than 7 days, and low-grade (99°–100°)	Commonly. Usually prolonged, and level may be higher (above 100°)
7. After-care required	None. Patient can return to full activity after collapsed lung has re-expanded	Continued bed rest and treatment of pulmonary tuberculosis

dyspnea and cyanosis are significant and are caused by the free pleural fluid, it is advisable to remove the fluid. The patient's underlying pulmonary tuberculosis must, of course, be treated.

Table 1 summarizes briefly the differences between benign idiopathic spontaneous pneumothorax and tuberculous spontaneous pneumothorax.

SUMMARY AND CONCLUSIONS

1. Benign idiopathic spontaneous pneumothorax and tuberculous spontaneous pneumothorax are two distinct entities with different causes, clinical pictures, and mortality rates. Cases of spontaneous pneumothorax must be carefully observed and the type or cause determined.

2. In a two-year period at one institution, 41 cases of benign idiopathic

spontaneous pneumothorax and 10 cases of tuberculous spontaneous pneumothorax were observed. Benign idiopathic spontaneous pneumothorax appears to occur four times as frequently as tuberculous spontaneous pneumothorax.

3. A table contrasts the two types of spontaneous pneumothorax.

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STUDIES ON THE SEQUELAE OF ACUTE INFECTIOUS HEPATITIS*

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Introduction

The widespread occurrence of infectious hepatitis throughout the world during the past several years has been the stimulus for intensive investigation of this disease. Great advances have been made concerning the etiologic, clinical and laboratory characteristics of this disease, particularly in its acute form. Different forms of sequelae have been described in the older and in the more recent literature. The variations in degree of severity have been wide— from asymptomatic, presumably innocuous, hyperbilirubinemia to disabling chronic cirrhosis of the liver.[1] Our interest in this problem has been the study of the natural history of the disease, with particular regard to types of sequelae as well as to their diagnostic and prognostic characteristics. The plan was the study of patients who had had infectious hepatitis during the recent epidemics, with regard to their subsequent courses.

Inasmuch as the demobilized military population offered the best reservoir for study, the project was established at the Bronx Veterans Hospital.

Methods

The study was begun in September, 1946, and the data to be reported represent the results obtained during the next 21 months. Case material was obtained from the investigation of previously hospitalized patients as well as those hospitalized currently. Most of the patients were seen periodically in the outpatient department, but many were studied in the hospital. Case histories were checked through Veterans Administration regional offices, hospital files, and with the individual patients in order to establish as complete continuity of the record as possible. Patients were examined carefully at each visit, with particular reference to evidences of liver disease. Laboratory tests were performed to evaluate stigmata of liver disease as well as the general health of the patients. Below are listed the specific laboratory tests used to estimate the status of liver function. The normal ranges for each procedure are noted with each test.

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Serum bilirubin (total) —0.1–0.8 mg. %
Icterus index —4–8 units
Alkaline phosphatase —1.0–4.0 Bodansky units %
5–15 King-Armstrong units %
Serum albumin —4.0–5.0 gm. %
Serum globulin —1.5–2.9 gm. %
Serum cholesterol —150–250 mg. %
Serum cholesterol ester —40–60% of serum cholesterol
Cephalin flocculation —0–1+
Bromsulfalein excretion—(5 mg./kilo read at 30 min.) 0–8%

In stated cases, appropriate roentgen-ray studies and other special procedures were done.

After the initial visit, the ambulatory patient returned to the clinic as directed, the symptomatology and physical examination were noted, and the laboratory tests were repeated. One hundred nine patients made one to 12 clinic visits, averaging three visits each, during the 21 month period of the study. The poor coöperation of many patients accounts for some gaps in the continuity of the data. Five patients were studied only in the hospital.

While under study in the clinic, the patients were advised to take a highly nutritious diet, similar to that described for the therapy of cirrhosis of the liver by Patek and Post.[2] For the source of extra vitamin B complex, Elixir B Plex (Wyeth) 30 c.c. daily or Therapeutic Formula Tablets (Squibb), 6 daily, were used. No other medication was employed. In the hospital the same dietary regimen was used along with bed rest.

Results

The 114 patients included in this report consist of 112 males and two females. The ages vary from 20 to 40 years.

With regard to the types of hepatitis, table 1 gives the information as accurately as could be determined.

Table I

Type	Number
Infectious hepatitis	108
Homologous serum hepatitis	3
Postvaccinal hepatitis (yellow fever vaccine)	2
Infectious mononucleosis hepatitis	1
	114

Fifty per cent of the patients contracted their illnesses in the United States, 33 per cent in the European War Theatre, and 17 per cent in the Pacific War Theatre.

The follow-up period in this series ranged from seven to 70 months after the onset of hepatitis. The average for the group is 22 months.

In the discussion to follow we have grouped the patients with sequelae as follows: those showing (1) recurrent jaundice, (2) persistent jaundice,

and (3) prolonged convalescence. Admittedly, this classification is artificial and may have no real biologic significance.

(1) The patient with "recurrent jaundice" recovered from the initial attack of hepatitis and at a subsequent date, after an interval of apparent well-being, redeveloped evidence of liver disease. In some patients the jaundice disappeared, but in others it persisted. This phenomenon of recurrent jaundice has been observed from one to three times in any one of the patients.

(2) The patient with "persistent jaundice" showed defervescence of the acute illness but continued to have jaundice for months or years thereafter.

(3) The patient with "prolonged convalescence" showed improvement after the initial illness but required four to 12 months before evidence of liver disease cleared. These three groups will be referred to throughout the presentation.

Symptoms

The symptomatology of the acute disease is perpetuated, in milder form, in the more chronic disease. The gastrointestinal tract is the area of reference. Nausea, occasional vomiting, upper abdominal pain, flatulence, pyrosis and anorexia were the chief complaints. Weakness, fatigue and malaise were frequent symptoms. During the first six to eight months of the study, 40 per cent of the patients had these symptoms. At the end of 21 months only 20 per cent had physical complaints.

We have noted that, as time passed and more satisfactory adjustment of the patients occurred, there was a defervescence in their symptoms. This does not imply that the symptoms are without significance.[3] Analysis of 23 patients with symptoms nine to 70 months (average, 34 months) after the first episode of hepatitis reveals that 15 had evidence of liver disease, having had at least one recurrence of jaundice. One patient had a prolonged convalescence (nine months) from the acute attack, and seven had no evidence of residua. It would appear that symptoms of the type described above, persisting many months after the initial illness, are frequently associated with lingering liver disease.

Weight Loss

Inasmuch as weight loss is a frequent finding in acute hepatitis, the body weights of these patients were investigated.

The reference point was a pre-sickness level at which the patient enjoyed good health. A weight loss of more than five pounds was considered of significance. There were 27 patients who were underweight by these standards seven to 60 months (average, 27 months) after the initial illness. The weight loss varied from six pounds to 41 pounds, averaging 16 pounds. Of these 27 patients, 10 had had at least one recurrence of jaundice, two a

prolonged convalescence, and 15 were free of stigmata of liver disease. It should be observed that most of the patients with sequelae were not underweight. Thus, the persistence of weight loss need not be associated with persistent liver disease.

Physical Signs

The chief physical signs, in the order of frequency, were icterus, palpable liver, spider angiomas and palpable spleen. Jaundice of the sclerae was noted in 17 patients seven to 56 months (average, 30 months) after their initial illness.

The liver was palpable in 11 patients seven to 60 months (average, 27 months) after their initial illness. It was tender in two patients. It could be felt 1 to 4 cm. below the right costal margin. Of these 11 patients, seven had evidence of lingering liver disease (recurrent jaundice), two had prolonged convalescence (seven and 12 months, respectively), and two seemed well. It would appear that a palpable liver in this patient population is usually associated with persistent liver disease.

Spider angiomas, in their usual locations, were noted in 10 patients, seven to 60 months (average, 27 months) after the initial illness. In six of these 10 patients there had been at least one recurrent bout of jaundice; in three, prolonged convalescence (seven to 12 months), and in the remaining patient, there was a palpable liver as the only other stigma of liver disease. It is apparent that spider angiomas are associated with lingering liver disease. It should be observed that most patients were unaware of the presence of spider angiomas.

The spleen was palpable in only three patients, 24 to 31 months after their first attack. These three patients showed evidence of recurrent icterus.

By way of summary, it may be stated that those patients demonstrating the palpable liver, spider angiomas and palpable spleen show a high incidence of chronic liver disease.

Laboratory Data

Icterus Index—Serum Bilirubin. Forty-four patients have shown raised levels of icterus index and/or serum bilirubin. Of these, 29 patients were considered to have recurrent jaundice, nine to have persistent icterus, and six to have prolonged convalescent states. The degree of icterus was usually mild, i.e., 10 to 30 units of icterus index, and 1 to 4 mg. per cent bilirubin, mostly of the indirect reacting type.

Cephalin Flocculation. Eighteen patients had positive tests seven to 70 months after the onset of the illness. Of these, 11 had evidence of recurrent jaundice, five prolonged convalescence, and two had no other stigmata of liver disease. Therefore, a positive cephalin flocculation test is usually associated with persistent liver disease.

Albumin-Globulin Partition. Only eight patients showed elevation in blood globulin seven to 40 months after the initial illness. Three of these patients had reduced blood albumin levels. Six of the eight patients had recurrent bouts of liver disease and were very ill. They represent the most seriously ill of the patients. One patient had a prolonged convalescence (seven months). One patient had a palpable liver, but no jaundice or other stigma of liver disease. As has been stressed before, the more markedly altered serum protein levels are usually associated with more severe liver disease.[4]

Other Tests. The alkaline phosphatase and bromsulfalein excretion levels were seldom abnormal. This experience with bromsulfalein is in accord with that of Kornberg,[5] but it is at variance with that of Kunkel [6] and Barker and Capps.[7]

The cholesterol-cholesterol ester figures were within normal range except in two patients. The hypercholesterolemia and hyperphosphatasemia in case 4 suggested the development of "cholangiolitic hepatitis," described by Watson and Hoffbauer.[8] Case 6 showed a reduction in the blood cholesterol.

Sequelae

We have considered sequelae under three headings: recurrent jaundice, persistent jaundice, and prolonged convalescence.

A. *Recurrent Jaundice.* Patients in this group seem to recover from their initial illnesses, with an interval of well being, only to have another episode of jaundice, with or without changes in other laboratory tests and clinical signs. Such an episode may be mild, without symptoms, and unknown to the patient. It may present itself as an evanescent elevation of blood icterus index or bilirubin, persist for some weeks, and then clear. On the other hand, jaundice may linger for months, and may be followed by a gradual deterioration of the patient with ensuing ascites and other serious changes.

Both single and multiple recurrences have been observed. In the 29 patients who comprise this group, the first recurrence occurred from two days to 43 months after the initial illness had abated (average, 16 months). Nine of these patients had a second recurrence nine to 56 months after the initial illness had cleared (average, 29 months). Three of these patients had a third recurrence 29 to 40 months after the initial illness had cleared (average, 34 months). The patients did not necessarily seem worse following a first, second, or even a third recurrence, nor did the severity of the recurrence within the same patient seem to be increased in its first, second or third occurrence.

From these data it appears that patients may be in good general health and subsequently may have repeated episodes of jaundice. Therefore, it seems that a single isolated series of liver function tests is an inadequate method for evaluating the patients' status, since many of these patients are

without abnormal tests for long periods of time. Only repeated testing and sometimes fortuitous timing of the testing may uncover evidence of liver dysfunction.

Below are listed several case histories to demonstrate the varying forms these recurrences may assume.

Case Reports

Case 1. This 20 year old veteran had the first attack of jaundice on March 22, 1945, while in Germany. He was hospitalized after a week. The course was uneventful and he improved. He was evacuated to the United States, where his convalescence continued. Below are given the laboratory data on this patient.

Date	Icterus Index	Ceph. Floc.	Cholest.	Ester	Alk. Phos. B. U.	A/G	BSP	Bilirubin
3–30–45	45							
4–13–45	10							
4–26–45	8							
5– 3–45	5.7							
8–29–45	17							
9–20–45	10							
9–24–45	10							
11–24–45	9							
1– 9–46	12							
2–20–46	4.5	1+						
2–21–47	9.8	1+	200	130	2.6	4.6/3.0	0	
5–20–47	9.3	0	145	68	2.5	5.3/3.1	0	
8–15–47	12.5	4+	160	120	2.2	5.5/2.2	10%	
10–24–47	10	0	170	90	2.2	5.5/3.4	0	
1–23–48		0						1 mg. %

It is of interest that on May 3, 1945, the icterus index was 5.7. Three months later it was 17, and then it continued to be slightly elevated for the next four months. In February, 1946, it was 4.5 and the patient was entirely free of disease. One year later he was well but the icterus index was 9.8. Six months later the icterus index was 12.5, with 4 plus cephalin flocculation and 10 per cent BSP retention. Thereafter icterus persisted. Hyperglobulinemia continued during 1947. This patient is without symptoms and is working, but hyperbilirubinemia persists almost three years after the first attack. He has shown at least two recurrences of jaundice, with free periods between, since his first illness.

Case 2. This 25 year old veteran had the first episode of jaundice in November, 1943, while in Oran, North Africa. It was described as mild and it lasted three weeks. He was not hospitalized. He was well until June, 1947, when jaundice recurred with malaise. He was treated at home and spent one month in bed. After four months of convalescence he was well and returned to work. He was in good health until mid-July, 1948, when he noted recurrence of jaundice. This was treated on an ambulatory status, but because of weakness, anorexia and a 41 pound weight loss he was hospitalized. Systemic inquiry was negative. Physical examination was negative except for scleral icterus. Laboratory studies showed: red blood cells, 3.8 million; white blood cells, 5,800; polynuclears 71; lymphocytes 23, monocytes 2, eosinophils 3; hemoglobin, 12.4 gm.; sedimentation rate, 2 mm./60 minutes; serology, negative; urinary urobilinogen, 1:640; icterus index, 12.5; serum bilirubin, 1.8 mg. per cent; albumin, 5.0 gm. per cent; globulin, 2.2 gm. per cent; cephalin flocculation, 2 plus; thymol turbidity, 3.5; cholesterol, 197 mg. per cent; cholesterol ester, 92 mg.

per cent; BSP less than 10 per cent at 30 minutes; red cell fragility, normal; reticulocyte count, 0.3 per cent. Roentgen-rays of gall bladder and chest were normal.

During the first five weeks in the hospital the patient was kept at bed rest and the bilirubin level fell to 0.8 mg. He was permitted up for one week and the serum bilirubin fell to 0.3 mg. The cephalin flocculation was negative. In view of his

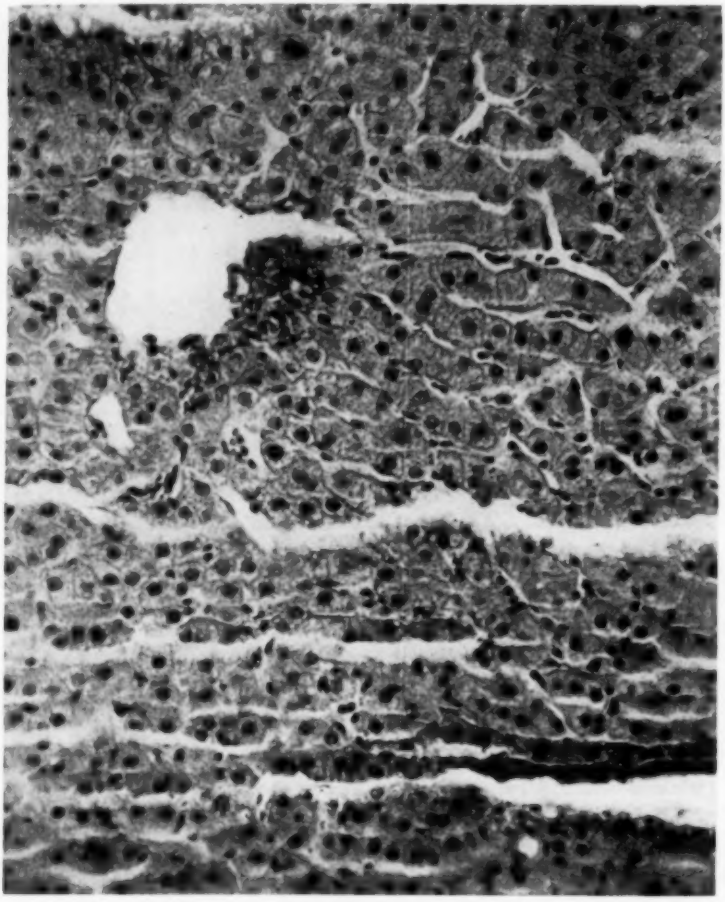


FIG. 1. *Case 2.* Liver biopsy 56 months after first attack of hepatitis. Normal liver is seen. 250×. H & E.

favorable course he was permitted to leave the hospital to return to the clinic. A liver biopsy performed during his hospital stay revealed normal liver tissue (figure 1). In spite of two recurrences of the disease, no histologic damage is demonstrable.

Case 3. This 24 year old veteran had infectious hepatitis in New Guinea in April, 1945, when he was hospitalized for two weeks. He felt well thereafter until

September 6, 1945, when symptoms of anorexia, fatigue, nausea and jaundice returned. He was returned to the United States in December and at this time the icterus index was 25. In March, 1946, it was 28. At that time liver and spleen were not palpable. He was discharged from the Army on April 25, 1946, with a diagnosis of chronic infectious hepatitis, and was transferred to the Bronx Veterans Hospital. Here the course was characterized by persistent icterus, malaise, and some tenderness over the liver. Cholecystography revealed a "poorly functioning gall-bladder" on April 26, 1946. The patient was discharged from the hospital December 19, 1946, and since then has been followed in the clinic. Below are listed the laboratory data obtained from April 9, 1946 to November 7, 1947.

Date	Icterus Index	Bilirubin	Ceph. Floc.	Alk. Phos.	A/G	Chol./Ester	BSP
4- 9-46	12.3		2+				
4-14-46	18.7		0				
5-23-46	30.0		0				
6- 3-46	33.0	3.2	1+				
6-10-46	21.6	2.7					0
7-12-46	19.5	2.8	0				10%
7-22-46	19.5	3.0	0				
7-29-46	22.0	3.3	1+				
8- 5-46	25.0		1+				
8-12-46	24.0		1+				
8-19-46	23.8		1+				
9-10-46	19.5	3.6	1+				
9-17-46	20.0		0				
10-24-46	27.2	2.2	1+	4.0 KA	5.3/3.0	222/142	0
1- 7-47	13.2	1.2	0	3.3 KA	5.1/2.6	168/108	0
3- 1-47	26.0	3.0	1+	2.6 KA	5.5/2.8	147/97	0
4-15-47	14.0	1.2	1+	0.9 BU	5.2/1.9	142/100	0
5-13-47	17.5	2.5	1+	1.5 BU	5.1/2.1	138/83	0
6-24-47	20.6	3.7	1+	1.5 BU	4.7/2.8	186/118	0
7-29-47	25.2		0	2.6 BU	5.7/2.7	156/91	
8-29-47	20.0	1.9	1+		5.3/2.3	160/126	
11- 7-47	21.2	2.4	0	3.6 BU	5.7/2.2	180/100	0

It is of interest that in January, 1947, telangiectases of the chest were noted. In June, 1947, a spider angioma was noted over the right clavicle. In April, 1947, a xanthoma of the inner canthus of the left eye was noted for the first time. This has persisted. There has been mild pruritus off and on. He has regained his weight and has been working regularly since discharge from the hospital.

Case 4. This 38 year old veteran was well until January, 1944, when he had an episode of nausea, vomiting, right upper quadrant pain, and jaundice lasting several weeks. He was in North Africa and sought no hospitalization. He had a recurrence of jaundice in June, 1945, lasting four weeks. He was hospitalized for this and improved. Again in March, 1946, he was hospitalized for jaundice, nausea, vomiting and abdominal pain. After one month he was discharged improved. On August 14, 1946, he was hospitalized at the Bronx Veterans Hospital for recurrent jaundice and swelling of feet and abdomen of one week's duration. The patient was a chronic alcoholic. Physical examination revealed a chronically ill, jaundiced, lethargic male. There were many spider angiomas over the neck, atrophy of the tongue, liver palpable 4 cm. below the right costal margin, spleen palpable just below the left costal margin, edema of the legs, and moderate abdominal distention with shifting dullness. Laboratory data on admission showed: red blood cells, 3.45 M; hemoglobin, 11.4 gm.; white blood cells, 6,800; normal differential; negative urinalysis; blood

urea nitrogen, 9.0 mg. per cent; blood sugar, 118 mg. per cent. Other studies are listed below:

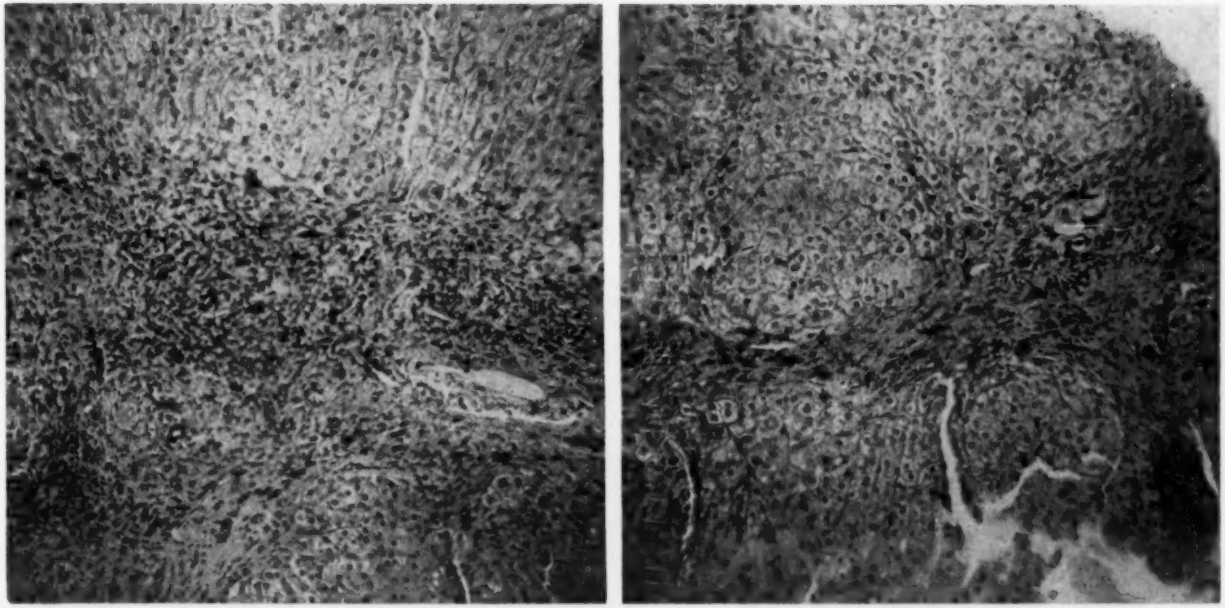
Date	Icterus Index	Bilirubin	Ceph. Floc.	A/G	Chol./Ester	Alk. Phos.	BSP
8–14–46	15.7		0	3.4/1.8	420/206	42.9 KA	
8–27–46	18.0	2.5		4.5/2.2	363/200	25.5 KA	
9– 9–46	6.0	less than 0.1	1+	4.8/3.2	320/188	17.2 KA	0

There was a gradual improvement under a regimen of bed rest and dietary therapy. On September 18, 1946, a liver biopsy was done. It showed inflammatory reaction about the central and portal areas, with round cell infiltration and fibrous tissue proliferation. The process was moderate. No fatty changes were seen (figure 2). The changes were compatible with chronic hepatitis.

Case 5. This 23 year old colored veteran was well until April, 1947, when he noted the onset of malaise, nausea, vomiting and jaundice. By June, 1947, he was well and returned to his work as a medical student. In September he had suppurative adenitis of the left arm, secondary to an infected finger. This was treated successfully with penicillin. In October, 1947, the jaundice and nausea recurred. He was hospitalized in November, when jaundice and abnormal liver function tests were found. He was transferred to the Bronx Veterans Hospital on February 17, 1948. At this time there was icterus and the liver was palpable 3 cm. below the right costal margin. The spleen was not palpable. During his hospital stay he remained underweight in spite of a high caloric diet, with vitamin B supplements. The jaundice persisted. Roentgen-rays of the stomach and duodenum were negative, and esophageal studies for varices were negative. The gall bladder failed to visualize on two occasions. In June, 1948, a liver biopsy was done through an abdominal incision. Many enlarged nodes were seen around the pancreas and common duct. The liver was grossly granular and yellowish-brown in color. The specimen of liver (figure 3) showed marked round cell infiltration about the central and portal areas, with connective tissue proliferation in these areas. The strands of connective tissue extended from central to portal areas, subdividing the liver into compartments. The liver cells were enlarged and frequently multinucleated and bile stained. Some bile duct proliferation was noted in the portal areas. The picture was compatible with coarse, nodular cirrhosis. Below are listed the laboratory data of the last few months.

Date	Icterus Index	Bilirubin	Alk. Phos. B. U.	Ceph. Floc.	A/G	ESR	Cholesterol
11– –47		3.1	7.0	4+	3.6/5.8	56	
12– –47		5.0					
2–20–48	18.3	1.6	2.3	2+	3.2/6.5	32	
3– 5–48	20.1	1.3	7.2			30	
3–16–48					3.7/5.8	29	
3–26–48	14.0		12.6	4+			
4– 6–48			8.7	2+	3.7/6.5		
4–12–48	14.5			3+			
4–22–48	39.0	4.2	7.3		3.2/6.6	29	
5–13–48	38.0	3.7	7.7	3+	3.6/6.8		250
5–26–48	31.5	4.1	14.7	3+	3.2/6.8	27	
6–22–48	22.6	2.1	11.6	4+			

2–20–48: RBC, 3.9 M; Hb, 12.0 gm.; WBC, 7,200; Platelets, 234,000.



A B

FIG. 2. *Case 4.* Liver biopsy 33 months after first attack of hepatitis. A. Periportal fibrosis, cellular infiltration, bile duct proliferation. 150×. H & E. B. Fibrosis involving central and midzonal areas. 150×. H & E.

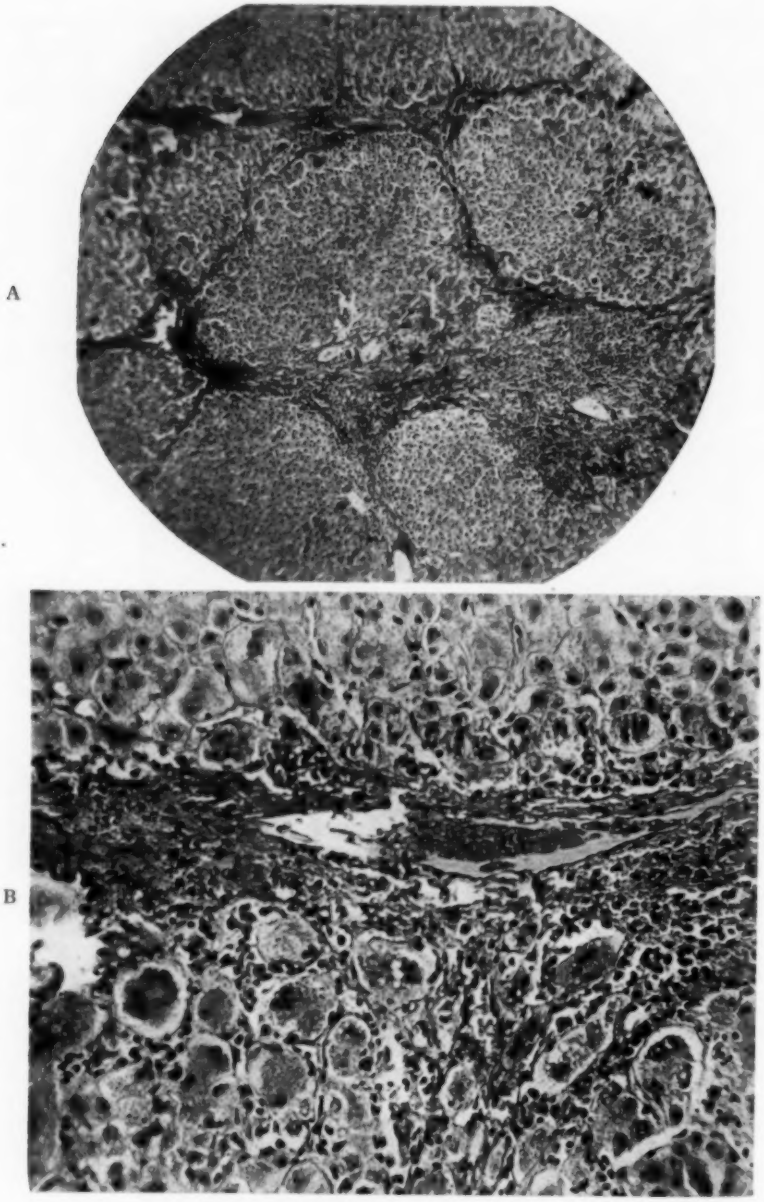


FIG. 3. *Case 5.* Liver biopsy 14 months after first attack of hepatitis. A. Coarse nodular cirrhosis. 50×. H & E. B. Fibrosis with cellular infiltration and large multinucleated liver cells. 250×. H & E.

This patient has shown progressive deterioration following a recurrence six months after the onset of the acute illness. The liver shows changes compatible with coarse nodular cirrhosis.

Case 6. This 23 year old female veteran received immunizing inoculations in May, 1945, and May, 1946, while in the U. S. Marine Corps. She became ill with ankle edema in August, 1946, and was hospitalized. Prior to that illness her health had always been excellent save for amenorrhea for five years. On admission she was found to have jaundice, ankle edema, palpable liver, and fever to 103° F. The serum albumin was 2.6 gm. per cent and globulin 3.1 gm. per cent; cephalin flocculation was 2 plus and icterus index 57. For the next 13 months her status remained essentially unchanged. She received human albumin at irregular intervals. Each time the serum albumin rose to normal with intravenous albumin and after discontinuing therapy it fell to the pre-treatment level. At discharge in September, 1947, the serum bilirubin was 1.6, albumin: globulin 2.6: 4.7, bromsulfalein excretion 20 per cent in one hour, and alkaline phosphatase 1.9 B.U.

She remained at home for two months, during which time her condition became worse. On November 22, 1947, she was admitted to the Bronx Veterans Hospital. She had had three days of diarrhea prior to her hospitalization. On admission she was vomiting and was very lethargic. Physical examination showed icterus, a moderate amount of ascites, 2 to 3 plus pretibial edema, marked liver palms, and many spider angiomas scattered over the arms and trunk. No abdominal organs were palpable. Laboratory studies showed: Albumin: globulin, 2.7: 3.4; red blood cells, 4,100,000; hemoglobin, 14.9 gm.; white blood cells, 7,600; normal differential; ESR, 21 mm./r.; cephalin flocculation, 3 plus; icterus index, 35; cholesterol, 100 mg. per cent; esters, 60 mg. per cent.

During the first few days she had fever to 104° F.; fetor hepaticus was marked, and increasing drowsiness became prominent. She received intravenous glucose, vitamin B complex and crude liver, but did not improve. She seemed to be in the terminal stages of liver disease. She was placed on intravenous albumin therapy as one of the first of a series of cases to be studied at the hospital. The next 36 hours brought a dramatic change. There was clearing of the sensorium to normal, brisk diuresis with loss of edema and ascites, and marked improvement in the general clinical appearance. The appetite returned. The patient was treated with albumin for the next three months, during which time the albumin level was maintained at normal and the hyperglobulinemia disappeared. Figure 4 shows her clinical course. Aside from a slight reduction in degree of icterus, all the tests, except for the protein levels, remained unchanged. After three months the therapy was stopped. During the next 10 weeks the albumin fell, the globulin rose, and edema returned. There was a return of weakness and malaise. After 12 weeks, albumin therapy was resumed and again there was loss of edema associated with a rise in serum albumin. Subjectively, the patient was much better. She has been maintained on albumin dosage sufficient to keep the level of serum albumin at normal (75 gm. once weekly). Her general condition seems good. The liver has become palpable since June, 1948. Liver biopsy in the fall of 1948 revealed advanced cirrhosis of the liver with coarse scarring, round cell infiltration, bile duct proliferation, and large islands of normal liver cells between scars. The picture suggested coarse nodular cirrhosis (figure 5). There is no longer any liver tenderness. She is up and about and seems to be more robust. It is felt that in this patient the disease has progressed to its most advanced stages. Albumin therapy seems to have been a life-saving measure, although the ultimate prognosis seems grave.

B. *Persistent Jaundice.* The second type of sequel is that in which the patient seems to remain icteric indefinitely after his initial illness has cleared.

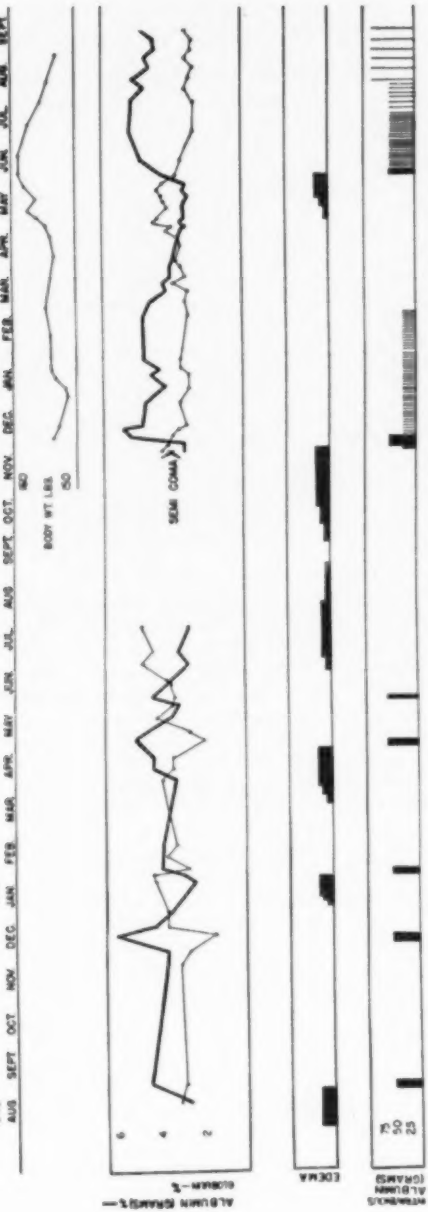


FIG. 4. *Case 6.* Clinical course showing diuretic effects of intravenous human albumin therapy.

The degree of icterus is mild. Some workers have considered three months as the upper limit for the duration of jaundice in the acute illness. Patients with more protracted jaundice are considered to have chronic hepatitis.[6, 7, 9] In the present study, nine patients have had jaundice persisting 15 to 31 months after the onset of the initial illness (average, 25 months). In these

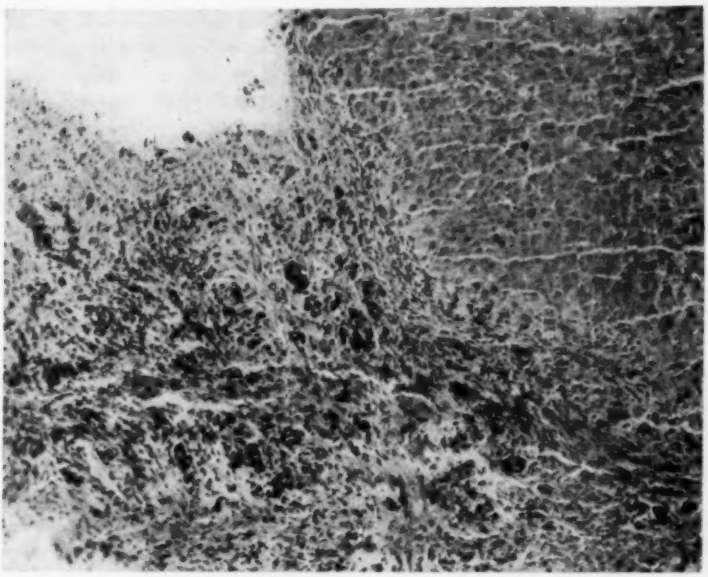


FIG. 5. *Case 6.* Liver biopsy 27 months after first attack of hepatitis. Coarse scarring with bile duct proliferation is noted. Liver cells are not remarkable. The picture is compatible with coarse nodular cirrhosis. 100 ×. H & E.

patients, jaundice may be the only measurable evidence of liver disease; in other respects the patients may be in good condition. Hemolytic phenomena have been excluded. Below is recorded the case history of one such patient.

Case 7. This 24 year old veteran developed jaundice in March, 1945, while in Germany. There had been one month of severe prodromal gastrointestinal symptoms. He was hospitalized on March 19, 1945, at which time the icterus index was 62, bilirubin 7.0 mg. per cent, and the liver was palpable 4 cm. below the right costal margin. By April 20, 1945, the bilirubin fell to 2.1 mg. Since that time the patient has had persistent low grade icterus. He was discharged from the Army in December, 1945. Since then he has been seen repeatedly at the Bronx Veterans Hospital. There has been mild right upper abdominal pain off and on. The liver and spleen were palpable from March, 1945, until June, 1946, but they are no longer palpated. The patient has been working for the past year and a half, and has been at his presickness weight for more than a year. Following are tabulated the data on this patient.

Date	Icterus Index	Serum Bilirubin	Cephalin Flocculation	BSP
3–23–45	62	7.0		
4–20–45		2.1		
5–18–45	9.8			
6–27–45	12			12%
8–29–45	30		0	17%
10–19–45	27		0	12%
12– 6–45	12		0	
1–18–46			2+	
1–23–46			2+	
2–18–46			0	
5–29–46	23.8	3.0		
6– 6–46	28	2.0	1+	
6–14–46	19.6	1.3		0
8– 8–46	14			
2– 4–47	16.3		1+	0

On February 4, 1947, alkaline phosphatase was 1.6 B.U., albumin: globulin was 4.5: 2.7, and cholesterol: ester was 192: 105.

This patient's jaundice has lasted for almost two years as the sole evidence of lingering liver disease.

C. *Prolonged Convalescence.* There is a third group of patients classified as having prolonged convalescence. These six patients have had stigmata of continuing liver disease for four to 12 months (average, eight and a half months) before the illness disappeared. Below is recorded such a case history.

Case 8. This 26 year old colored veteran developed jaundice on November 25, 1946, after one month of malaise and abdominal pain. He was hospitalized on November 26. At that time there were scleral icterus and tenderness in the right upper quadrant. The body weight was 10 pounds below normal. There was gradual disappearance of the jaundice, and after six weeks he was discharged to the clinic. Below are listed the pertinent laboratory data.

Date	Icterus Index	Serum Bilirub.	Ceph. Floc.	Alb./Glob.	Alk. Phos. B. U.	Chol./Ester	BSP
11–26–46	55.0	4.2	0				
11–29–46	40.0		0	4.1/2.3			
12– 3–46	8.6		1+				
12– 6–46	9.0						
12– 9–46	16.0						
2–21–47	10.0		1+	4.6/3.7	2.7	200/126	0
5–27–47	6.6		0	5.0/2.4	3.3	135/70	0
8–15–47	10.2		3+	5.3/2.6	2.4	210/151	5%
11–21–47		0.6	0		2.5	145/83	0
3–19–48		0.1	0				

This patient showed rapid defervescence of icterus during the initial phase of the disease, with more gradual clearing thereafter. It was 12 months before the hyperbilirubinemia disappeared and the cephalin flocculation test became normal. His weight returned to its pre-sickness level during this 12 month period.

Of the group of 44 patients with sequelae, four showed changes compatible with clinical cirrhosis of the liver. Case 4 had edema, ascites, and extensive collateral venous circulation over the anterior abdominal wall. The liver biopsy revealed periportal and pericentral fibroses, consistent with chronic hepatitis. Case 6 showed edema and ascites with hypoalbuminemia. Liver biopsy revealed changes compatible with coarse nodular cirrhosis. Case 5 had no edema or ascites, but liver biopsy revealed well advanced coarse nodular cirrhosis of the liver. A fourth patient, whose case is not presented, had ascites, and liver biopsy showed coarse nodular cirrhosis. These four patients represent about 9 per cent of the group with sequelae and about 3 per cent of the entire group of patients studied.

This incidence may be excessively high when it is considered that our sampling of the general hepatitis population is statistically inaccurate. Many patients in this study were referred to the hospital because of continued illness. This would introduce a large error in any statistical evaluation of the incidence of sequelae.

Factors Possibly Related to Sequelae

The records of patients with sequelae have been reviewed in search of factors which could have contributed to the occurrence of sequelae. It has been stated that the incidence of sequelae might be reduced if the acute illness were adequately treated with regard to optimal nutrition and rest.[6, 7, 10] Polack has stated that intercurrent infections may be associated with recurrent jaundice.[10]

With regard to the treatment of the acute illness in these patients, the data are incomplete inasmuch as most patients were not observed by the authors during this phase of their illness. Below are listed the factors which may have played some rôle in the sequelae noted in the 44 patients.

Table II

Malaria	3
No hospitalization for first attack of hepatitis	2
Brief hospitalization (15 days or less) for first attack of hepatitis	3
Progressive muscular atrophy	1
Right pleural effusion (sterile)	1
Alcoholism	1
Suppurative adenitis	1

Malaria might be considered in the group of "intercurrent infections" cited by Polack.[10] Indeed, there are some workers who maintain that malaria, per se, produces liver dysfunction.[11, 12] However, there is disagreement on this point.[13, 14, 15] In the patients reported here the evidence for previous hepatitis was conclusive, and the exacerbations of jaundice with the attacks of malaria outlasted the successfully treated malaria by weeks. The patient with pleural effusion might be considered in the group of "intercurrent infections," as might the patient with suppurative adenitis. In five patients, inadequate or no medical care during the acute phase of the disease may have

been important in providing a basis for chronic liver disease. The patient who drank heavily (case 4) showed marked clinical deterioration. The liver biopsy showed changes consistent with chronic hepatitis rather than Laennec's cirrhosis. In this patient, alcoholism and malnutrition may have contributed to perpetuating the disease.

The general health of the other patients, aside from their liver disease, was remarkably good during the 21 months of study. The usual acute respiratory tract infections and the mild diarrheas were weathered without difficulty.

In summary, while some of the factors enumerated may have contributed to the perpetuation of the liver disease, there remain about 75 per cent of the entire group of patients with sequelae for which no explanation is evident.

Discussion

Most patients with acute hepatitis recovered uneventfully. However, in some patients sequelae occurred. These consisted largely of persistent or recurrent mild jaundice. Some patients demonstrated palpable livers, spider angiomas, and positive cephalin flocculation tests. Sometimes the symptoms were difficult to evaluate; however, it would appear that when they lasted for many months (nine to 70) after the acute illness, they were usually associated with chronic liver disease. In 60 per cent of the patients with sequelae no symptoms were noted. The clinical state of the patient with sequelae was compatible with normal activity in most instances. Four patients had severe disabling liver disease which seemed to progress rapidly during the first year after the onset of the acute disease. Cases 5 and 6 demonstrated these changes as well as the advanced histological lesions (figures 3 and 5). Other authors have shown that hyperbilirubinemia or delayed bilirubin excretion tests may occur from months to years after the acute illness has subsided. They have observed that this state may be compatible with good health.[5, 6, 17]

The cause of the abnormal bile pigment metabolism is unknown. From case 2 it appears that recurrent jaundice is compatible with normal liver histology (figure 1) 56 months after the initial illness. Flood and James [9] have shown that chronic icterus of 18 months' duration may occur in the presence of a normal liver biopsy. Watson and Hoffbauer [8] have stressed the meager histologic changes in some of their cases of "cholangiolitic hepatitis," and they have stated that "a severe functional derangement of the cholangioles, and to a lesser extent of the liver cells, may be present though not microscopically apparent."

These data indicate that the injury incurred during the acute illness may damage the liver functionally without altering its structural appearance. The analogy in the case of the hepatic storage of vitamin A seems pertinent. Carbon tetrachloride-induced cirrhosis of the liver in rats is associated with

a marked reduction in storage of vitamin A. When the hepatotoxin has been withdrawn for three months, the liver regenerates so that there is almost complete histologic restitution to normal. Yet at this stage the storage of vitamin A in the liver is still markedly reduced, less than 50 per cent of normal.[18, 19] Thus, considerable physiologic disorder may occur without observed accompanying histologic changes.

The causes of the sequelae are obscure. The treatment of the acute illness may play a major rôle in the future well-being of the patient. In the present study, only about 25 per cent of the patients seemed to present some factor which might have contributed to the continued liver disease. In the remainder of the patients with sequelae no clues could be found. Although we have seen seemingly new infectious hepatitis recur years later in the same patient, it is doubtful that each recurrence observed in these patients represents a re-infection with a new, antigenically specific virus.

It has been suggested that the virus of the original infection remains active within the host after the acute disease subsides. Oliphant et al.[20] could not demonstrate active virus in the blood of patients two and a half months after jaundice had cleared. Neefe et al.[21] were unable to prove the presence of active virus in the livers of patients with chronic hepatitis months after the acute illness.

Another possibility is that the initial injury to the liver produces certain functional changes which may persist at a clinical or subclinical level. With the passage of time these changes may progress and anatomic changes may occur. In the course of the disease, remissions and exacerbations are seen along with latent periods. In this respect the disease resembles chronic glomerulonephritis.[22, 23, 24] In evaluating the status of the patient who has had acute hepatitis, repeated clinical and laboratory studies are necessary. An isolated test may fail to reveal any abnormalities.

The treatment of the sequelae has been empirical, based on that of Laennec's cirrhosis.[2] In most patients improvement is noted. Because of the "spontaneous" fluctuations in the course of the disease, it is difficult to ascribe effects of therapy to specific agents. In case 6, intravenous human albumin seemed to be a life-saving measure. However, this may be of temporary benefit.[25] The reports concerning the use of methionine must await confirmation.[26] Such studies must be considered against the background of the natural history of infectious hepatitis.

Summary and Conclusions

1. One hundred fourteen patients who had acute infectious hepatitis were observed during a 21 month period, from seven to 70 months after the acute illness. Most patients recovered completely.

2. Gastrointestinal symptoms were the most common physical complaints. When these persisted for nine to 70 months after the acute illness they were usually associated with chronic liver disease.

3. Jaundice, palpable liver and spider angiomas were the most common physical signs associated with chronic liver disease.

4. Elevated icterus index and/or bilirubin and positive cephalin flocculation reaction were the most commonly encountered abnormal laboratory tests.

5. Of 44 patients with evidence of sequelae, 29 had one to three recurrences of jaundice, nine had chronic jaundice, and six had prolonged convalescent states.

6. Recurrent jaundice (twice) is compatible with normal liver histology 56 months after the acute illness. On the other hand, cirrhosis of the liver may develop 14 months after the initial illness.

7. Repeated observation and testing seem essential to the adequate evaluation of the patient who has had acute infectious hepatitis.

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ROCKY MOUNTAIN SPOTTED FEVER ON LONG ISLAND *

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THE conquest of bacterial incitants of disease has been so successful that medical research is being directed more to viral and rickettsial diseases. Agents in these latter infections are not only complex because of their ultramicroscopic size and obligate parasitic enzyme systems, but some are transmitted by arthropod vectors. Thus, they are influenced by their ecology. An endemic focus of Rocky Mountain spotted fever has been known to exist on Long Island since 1912 and has remained limited to the island. It has afforded an opportunity to study an arthropod-borne disease.

Rocky Mountain spotted fever is an acute infectious disease caused by *Rickettsia rickettsii*, which is transmitted to man by a tick. It is characterized by fever and a maculopapular rash that commonly appears first on the extremities. The basic pathologic picture is an acute diffuse endoangiitis that causes the characteristic rash and, often, subsequent petechiae and ecchymoses, the central nervous system symptoms, and the cardiovascular impairment. There is an effective vaccine prepared from rickettsiae cultivated in the yolk sac of embryonated chicken eggs and, recently, effective therapy has been found in para-aminobenzoic acid and, even more effective, in aureomycin and chloromycetin.

Although seven species of ticks have been identified within the area,[1] the American dog tick, *Dermacentor variabilis* (Say), is the only species that consistently attaches itself to man and is, presumably, the principal vector of spotted fever on Long Island. The epidemiology of the disease depends on the distribution, biology, ecology, and control of this tick. How did this disease develop on Long Island? What factors maintain it there? How can the disease be controlled or eradicated? Before attempting to answer such questions certain facts about this tick should be presented.

First, the pathogenic rickettsiae are innocuous to the infected tick, and they are transmitted from the gravid female to her eggs, from which infected larvae develop. The rickettsiae are retained as the larva moult into nymphs and then into adults.[2, 3, 4] Thus, the tick is not only the vector but a reservoir of the disease. Secondly, nymphs and adults are capable of surviving cold weather and live from year to year. These characteristics of the tick are the primary factors in maintenance of a focus.

In addition, continued multiplication and metamorphosis of the tick through the four-stage life cycle depend upon a certain length of optimum

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climatic conditions, such as the long, warm, humid days of summer and the presence of suitable flora and fauna. Animals are essential, because a blood meal is the tick's only source of food and is necessary for the development of eggs in the gravid female and for the metamorphosis of the other three stages. On Long Island, small rodents, such as the white-footed field mouse, are the common host of larvae,[1] while nymphs and adults are found on a number of mammalian species, particularly dogs, foxes, and raccoons,[1] in which specific complement-fixing antibodies were demonstrated in high titer. The spleens of nine species of mammalian hosts were inoculated into guinea pigs without recovery of specific rickettsiae or production of specific complement-fixing antibodies.[5] The disease was not induced in six foxes and two raccoons infected with the highly virulent Bitterroot strain, but complement-fixing antibodies were produced. Four weeks after inoculation, the spleens of these experimentally infected animals induced no reaction in guinea pigs. Transient infections demonstrable only serologically are possible, but infectivity of host tissues for any significant period is doubtful. However, if, as Ricketts[6, 7] observed, hereditary transmission does not take place in more than 50 per cent of infected female ticks, in time this alone would result in disinfection of the tick population. Since the disease is endemic, there must be a source of replenishment of the rickettsiae in the vector, presumably through animal reservoirs. It may be that if a feeding infected tick incites a transient infection of the host's blood, a sterile tick feeding simultaneously may become infected.

The following factors probably contribute to the tendency of this endemic focus to remain static. In infected but dormant unfed ticks the number and virulence of the rickettsiae will decrease. Long field activity, particularly, without a blood meal, results in the death of the majority of the adults of any one season. For example, 300 adult ticks were held in captivity on local flora with a wire cage. They had the same ecology as other ticks, except that they did not have access to hosts. By the end of the summer only three ticks (1 per cent) were still alive. Unfed larvae usually die within a month of starvation.[8] A conceivable but yet undemonstrated factor in maintaining a static focus is that the incidence of infected eggs may decrease with succeeding generations. The late Dr. R. R. Parker[9] wrote as follows: "It was well over 20 years ago that I initiated a study to determine through how many generations the rickettsiae would persist and what percentage of offspring would be infected. However, we ran into difficulties and the study was never completed." Ricketts in some unfinished experiments recorded by Davis[7] fed and mated females on infected guinea pigs and then refed some on immune guinea pigs, others on normal pigs. He found that eggs from gravid females fed on immune animals appeared to have a lower incidence of infection than eggs from infected females feeding on normal pigs. Actual counts were not made, and this was an assumption by the examiner, Dr. Marie Maver. This important factor needs thorough investigation. In

this connection, Travassos [10] claims that serial passage of a virulent strain of *R. rickettsii* through a species of Brazilian opossum results in a strain avirulent for guinea pigs. Ricketts thought that virulence of a strain might be altered by passage through species of ticks not commonly its vector, but his untimely death prevented his demonstration of this hypothesis and no proof to date has been presented. This, too, needs investigation.

How the ticks and the disease were introduced to Long Island is not known. The first reported case of spotted fever occurred in May, 1913. The 49 year old game keeper on Gardiner's Island removed a tick from his foot on May 1 and on May 5 he had a slight headache and pains in his back and extremities. On May 9, his wife noted a rash on his wrists and ankles that resembled the rash she had during a febrile period the summer of 1912. Dr. David Edwards, who is still practicing in East Hampton, attended the case and found that the owner of Gardiner's Island had been ill in the summer of 1912 with headache, fever, and rash. Dr. Van Dine, of the United States Public Health Service, who investigated these first three cases, stated in his report [11] that five years previously, in 1908, a certain Colonel Wagstaff had been bitten by a tick on Long Island and developed "blood poisoning."

An extensive search was made for evidence of the disease prior to 1908 in the East Hampton Library, which houses the Pennypacker Collection of some 120,000 historical documents concerning Long Island and includes journals of the Gardiner family, physicians' diaries and textbooks, and death reports kept by the clergy of the parish. In addition, an examination was made of the vital statistics reports of East Hampton [12] and Southampton.[13] Source material examined covered the eighteenth and nineteenth centuries, and special attention was directed to references to epidemics and deaths related to diseases characterized by exanthemata and other skin lesions. An attempt was made to detect a seasonal incidence of such diseases. No evidence was found to indicate that Rocky Mountain spotted fever existed on Long Island prior to 1900. Reference to typhus fever was found as early as 1849, and in May, 1882, there was a fatal case of typhus fever in Southampton. These could have been cases of Rocky Mountain spotted fever, but true epidemic typhus was known at that time.

The first definite reference to ticks occurred in an article written by C. M. S. in the "Eagle," August, 1898 (the clipping does not reveal the site of publication).[14] In it, the reporter describes the tick infesting the bivouac area of Colonel Roosevelt's Rough Riders on the southeastern peninsula of Long Island in 1898. It reads as follows: "It was the size of a bed bug and he lives in the grass and he crawls up into your clothes and you find him living next to you and tear him off and squeeze him between your thumbnails and he utters a Ha, Ha of derision and slips off to explore you in a new place and he is no thicker than a sheet of paper and he is as tough as the sole of your shoe and he gorges on your gore and he is going to be unpopular." Two mentally alert residents of Long Island, 79 and 84 years of age,[15, 16]

gave descriptions of ticks in Southampton in 1875 and on Montauk peninsula in 1880 which definitely coincide with the characteristic features of *D. variabilis*. This discounts the theory that the ticks were introduced to Long Island on the horses of the Rough Riders. In 1890, the caretaker of Gardiner's Island claimed that a horse died of a heavy tick infestation.[11]

It has been suggested from time to time that the ticks were brought from the west on certain infested horses and buffalo, but no evidence to substantiate this was found. In fact, an article in the East Hampton *Star* [17] states that two of three imported buffalo had been obtained in Nebraska in 1893 but were exhibited at the Chicago Exposition for one year prior to transfer to Long Island. The third buffalo was shipped from Kansas in October, 1893, but the long train ride necessary at that time makes it somewhat doubtful that attached live ticks remained on this animal. Search reveals that the horses were imported from New Mexico but prior to arrival remained for some time in an armory in New York City. Further inquiry indicates that such importations were very limited.

During our field survey, 74 birds, of 26 species, mostly ground-inhabiting types, were examined for ticks. None had *D. variabilis*.[1] These observations cast doubt on the assumption that the tick was introduced by migratory birds.

During the period from 1912 to 1949, approximately 160 cases of spotted fever have been reported (table 1). Analysis of these cases reveals no significant clinical difference in the eastern and western forms of the disease, although Davis,[18] in a study of 30 cases admitted to the Southampton Hospital with a mortality rate of 30 per cent, found that splenomegaly, leukocytosis and cutaneous necrosis were less frequent than in the reported western cases. The case prevalence parallels the prevalence of the ticks during the months of May, June, July and August (table 2). It is interesting to note that cases

TABLE I

Rocky Mountain Spotted Fever on Long Island
1912–1949

Year	1912	13	24	26	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	Total
Cases	2	1	1	1	1	1	3	4	2	1	2	5	12	0*	8	9	15	18	14	16	18	18	9	159
Deaths	0	0	0	0	0	0	0	2	1	0	1	1	2	0	2	1	1	4	2	4	1	1	0	23

1912–1943 Deaths: 11– 6 females; 5 males.
Cases: 68–32 females; 36 males.
1944–1949 Deaths: 12– 8 females; 4 males.
Cases: 91–46 females; 45 males.

* The following hypothesis is offered for the absence of cases in 1940: The hurricane of 1938 temporarily inundated wide areas of eastern Long Island and the majority of small rodent hosts of the larvae of *D. variabilis* were probably drowned. Nymphs and adult ticks survived and were the vectors spreading the disease in 1939. However, larvae developing from their eggs did not find sufficient small rodents for the blood meals that are essential for metamorphosis to nymphs. As a result, in 1940, there was a paucity of adult forms to infect the human population. Only an experimental field study will provide proof of this thesis.

occurring early in the spring or in the fall were associated either with unusually warm springs or falls or with dogs. The dog, in roaming over wide areas, collects and brings into the house a higher number of ticks than would otherwise be encountered by man at such times. Cases were divided equally according to sex (table 3). Half of the cases occurred during the first two decades of life, during which the mortality rate is lowest. This accounts for

TABLE II

Rocky Mountain Spotted Fever on Long Island
1912–1949

Month	April	May	June	July	August	September	October	November	Total
Cases	5	28	43	45	32	3	2	1	159
Deaths	1	4	8	7	3				23

Five of the cases occurring after August and one case in April were associated with family household dogs. It is stated that the spring of 1945, during which there were three cases in April, was unusually early.

the low mortality rate in the east, whereas in the west, approximately 50 per cent of the cases occur in persons over 40 years of age. There it is an occupational disease of woodsmen, ranchers and sheep herders. On Long Island it is a disease of residents and persons on vacation. Of the 107 cases reported between 1941 and 1949, 15 cases were contracted on Long Island

TABLE III

Rocky Mountain Spotted Fever on Long Island
1912–1949
Case fatality rate

Age	1–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	Total
Cases	59	23	12	11	21	14	13	6	159
Deaths	3	0	3	2	4	5	2	4	23
Male	1	0	1	0	2	1	2	2	9
Female	2	0	2	2	2	4	0	2	14
Case fatality rate—%	5	0	25	18	19	36	15	67	14.5
Sex distribution									
Male	25	18	5	5	10	8	7	3	81
Female	34	5	7	6	11	6	6	3	78

but became ill in metropolitan New York. It has been surprising that so few of the hundreds of thousands of vacationing metropolitan population develop the disease. Analysis of the 15 cases shows that the date of onset of 12 was on or after June 27. The incidence of ticks reaches its peak in middle or late June and drops rapidly thereafter. Local parks and camps do not open or have a small attendance before July 4. Therefore, the metropolitan popu-

lation is in the endemic area at a time when the tick population is disappearing.

The eastern end of Long Island terminates as two diverging peninsulas. On the southern peninsula there are extensive areas of woods and uncultivated land. Here the first case appeared on the mainland in 1924. Thirty cases from the area were in the Southampton Hospital between 1933 and 1946, with a case fatality rate of 30 per cent, as compared with approximately 17 per cent for the entire endemic area. The northern peninsula has been under extensive truck gardening for years and here only one case has been reported. A high state of cultivation eliminates favorable flora and animal hosts for the tick and is a means of controlling the vector of this disease.

The use of para-aminobenzoic acid, chloromycetin, and aureomycin probably accounts for the decrease in case fatality in 1947, 1948 and 1949 (table 1). While a course of three inoculations of vaccine, seven to 10 days apart, one month before the beginning of the season will usually give immunity in children, in adults this may only ameliorate the disease the first year. One case in 1948 had been vaccinated the previous year but did not get his first booster dose in 1948.

It appears doubtful that a significant amount of subclinical disease exists within the focus. Sera from over 300 normal persons without a clinical history of spotted fever were examined for complement-fixing antibodies. Seventy per cent gave no reaction and only 10 sera had appreciable reactions, the highest titer being ten 50 per cent units of fixed complement. Although the complement-fixation test is a more specific serodiagnostic test and at times detects the disease earlier, the Weil-Felix test remains very valuable and both should be used. Neither appears to have much application in the measurement of protection from active immunization with vaccines.

Although vaccination and antibiotic therapy provide a defense against the disease, reducing morbidity and case fatality, the control and reduction of the disease require an offensive attack on the tick vector which, for reasons set forth before, probably constitutes also the principal reservoir of the disease. Creation of an unfavorable ecology by elimination of hosts and alteration of soil and flora is not only a most difficult task but might have disastrous effects on local ecology. However, it has been shown that development of a natural area into urban and cultivated zones is effective in reducing the ticks. Burning off of areas is only temporarily effective, because ticks and mice move in from the perimeter of the burned area as soon as new growth starts.

The dog, man's closest associate among the vector's hosts, is often heavily infested and is the means of bringing large numbers of ticks into contact with man. In the process of removing ticks with bare fingers infection may occur, particularly from crushed engorged females. Restriction of dogs in camps and homes within tick-infested areas and proper removal of their ticks reduce danger of accidental infection.

The newer acaricides now afford a most effective offensive attack. DDT, in concentrations that do not harm flora and insects, will kill all stages of *D. variabilis*.

During 1949, the staff of the office of the New York State entomologist, under direction of Dr. Donald Collins, made an attempt to control the tick population of Shelter Island, an area of 12 square miles with some 135 miles of roads, paths and trails traveled by man and bordered by tick-infested flora.

Experience had shown that application of an acaricide by a spray delivered by airplane is not only expensive but unnecessary in control of ticks. However, the helicopter promises to be an effective mechanism for control of biting insects, such as the black fly, because the down draft of its rotors drives the acaricide through the trees and even under leaves on the ground. Its capacity to hover off an area is a valuable feature.

The tick is attracted to the sites of mammalian travel by the scent of man and animals. For example, mice captured at the edge of a road will be three times as heavily infested with ticks as mice taken 100 feet back, and eight times as infested as mice trapped 200 feet back.[19] Thus, the great majority of ticks are concentrated within narrow lanes on each side of paths of animal and human travel. Therefore, the 135 miles of roads and paths on Shelter Island were sprayed with a 5 per cent DDT aqueous solution in amounts to give about five pounds per acre. Two and one-half per cent solutions are equally effective. The spray was applied on each side for a distance of four to 10 feet. On passable roads a jeep-mounted spray apparatus was used, otherwise, a hand-operated and transported sprayer was used. The first application was made in June, to destroy nymphs and adults surviving the winter when ticks were at their greatest incidence. There is a residual action on ticks entering the sprayed area for approximately three to four weeks. A second application, to destroy the larval forms developing from eggs laid during the season, was made in August.

The effect was determined by counting the number of ticks in selected linear, 100-yard zones along roadsides before and after spraying. Ticks were collected weekly by dragging a square yard of white flannel over the ground. Before spraying, 200 or more adults per 100 linear yards were found. The ticks were redistributed in the dragged area. After spraying, not more than two to three adults were found alive in the same area. In control, unsprayed areas on the mainland, the tick population was maintained at a high level through the early summer.

The results to date indicate that *D. variabilis* can be effectively controlled by the acaricide, DDT. The effect of such measures on the incidence of the disease on Long Island must await further observation in subsequent seasons and their more widespread application.

In summary, we do not know how the American dog tick was introduced to Long Island, but there is evidence that the tick existed there between 1875 and 1898, a number of years before the first clinically proved case, which oc-

curred possibly in 1908 and definitely in 1912. The disease on Long Island is not significantly different from the disease in other parts of the United States. The case fatality rate of 14.5 per cent is less than in the western United States because of the higher incidence of the disease in the first two decades of life when mortality is low. There is no real evidence that the human disease is increasing in this focus. Apparent increase in case incidence can be attributed to better diagnosis and reporting and to increase in the number of persons exposed to ticks.

The tick, *D. variabilis*, is not only the vector but probably the principal reservoir, because, first, the pathogenic rickettsiae are transmitted transovarially from generation to generation and from stage to stage; and, second, the animal hosts of the tick probably are very transiently infected, if at all, by the pathogenic rickettsiae.

While prophylactic vaccination and antibiotic therapy are materially reducing morbidity and mortality, the most effective means of control and eradication of the endemic focus of Rocky Mountain spotted fever appear to be the widespread application of acaricides, such as DDT, along routes of human and animal passage.

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THE TREATMENT OF AMEBIASIS, WITH A PRELIMINARY REPORT ON THE USE OF AUREOMYCIN *

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ADEQUATE therapy of amebiasis—the human infection by *Endamoeba histolytica*—demands treatment of possible systemic as well as intestinal infection.[1, 2] Since the use of ipecac early in the Nineteenth Century, the search for more effective drugs has continued; however, despite introduction of improved therapeutic agents, a significant failure rate and also a definite incidence of toxicity have not been eliminated.

Drugs which have been used against amebiasis include:

1. *Emetine group*—ipecac, emetine, and emetine bismuth iodide.
2. *Oxyquinoline derivatives*—Chiniofon, Vioform, Diodoquin, Chloroquine, Win 246 and Win 1011.
3. *Organic arsenicals* (pentavalent arsenicals)—carbarsone, Treparsol, Acetarsone. (The trivalent analogues of carbarsone with substituted sulfhydryl groupings—the thioarsenates—have been proposed by Anderson.[3])
4. *Others*—including Kurchi bark, mercury and silver salts, quinine, etc. More recently, attention has been drawn to the antibiotics, bacitracin and aureomycin.[4]

At Veterans Administration Hospital, Lincoln, Nebraska, a small series of patients with amebiasis has been treated with aureomycin, as first proposed by McVay, Laird and Sprunt.[5]

Except for chloroquine and Win 246 (the 7-iodo analogue of chloroquine),[6] none of the oxyquinoline derivatives or arsenicals compares with emetine in effectiveness against extra-intestinal amebiasis. A frequently employed therapeutic routine has been a combination of emetine, carbarsone, and the iodine-containing oxyquinoline drugs.

Review of records of this hospital from October, 1947, to October, 1949 (when the above treatment routine was used), indicated 140 patients who had 158 admissions during which positive stools were demonstrated. All except two of the recurrences appeared within five months after treatment, and the recurrence rate was 11.5 per cent.

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Some writers state that emetine toxicity has been overemphasized, because few clinical reports of toxic effects followed the numerous amebic infestations treated during and after the war. However, review of cases treated with emetine at this hospital suggested the toxicity has not been overstressed, but is often overlooked. Thirty-five patients had serial electrocardiographic studies adequate for evaluation of possible myocardial change. Twenty-two had normal tracings after emetine was completed; 13 (37 per cent) had abnormal electrocardiograms, of which three (8 per cent) were

TABLE I

EKG Changes Following Emetine

	Age	Cardiac History	EKG before Treat.	Amount Emetine (grains)	EKG at End of Treat.	EKG One Month or More Later	Symptoms
1	28	None	Normal limits	5	Abnormal	Normal limits (6 weeks)	None
2	52	None	Normal limits	4	Normal limits	Abnormal (3 months)	Exertional dyspnea
3	27	None	Normal limits	5	Abnormal (IV block)	No data	No data
4	21	None	Normal limits	6	Abnormal (IV block)	Abnormal (IV block) (6 weeks)	None
5	22	None	Normal limits	6	Abnormal	No data	No data
6	36	None	Normal limits	6	Abnormal	No data	No data
7	62	Short of breath	Coronary insufficiency	12	Abnormal (LBBB)	Abnormal (LBBB)	Same
8	27	None	Normal limits	9	No data	Abnormal (6 weeks)	Dyspnea
9	22	None	Normal limits	9	Abnormal rhythm and P waves	Abnormal (Ant. wall damage) (6 weeks)	Tachycardia
10	26	None	Normal limits	6	Abnormal	Normal limits (6 weeks)	None
11	32	None	No data	5	Abnormal (LBBB)	Normal limits (6 weeks)	None
12	25	None	Normal limits	9	Abnormal	No data	No data
13	55	None	Normal limits	5	Abnormal	No data	Dyspnea (6 weeks)

significantly abnormal six weeks or longer after completion of emetine therapy.

Eight patients were observed for evidence of liver damage following emetine-carbarsone therapy. Seven had negative cephalin flocculation tests prior to treatment. Five had 2 plus or higher reactions after emetine, and one was still elevated after six weeks.

The report by McVay and colleagues on aureomycin aroused hope that effective treatment of both systemic and intestinal amebiasis might be accomplished with a nontoxic agent. They noted that patients receiving aureomycin for other infections developed alteration of gross stool character

and reduced fecal bacterial flora. Possible action against *E. histolytica* was suggested. In vitro, amebae were inhibited in six hours in aureomycin concentrations of 0.8 mg. per c.c. to 3.2 mg. per c.c. McVay treated 14 patients, and reported stools after aureomycin to be repeatedly negative.[8]

Fuller and Faust [7] attempted substitution of aureomycin for other antibiotics (penicillin and streptomycin) in culturing *Endamoeba histolytica*. They reported amebae to be completely inhibited, either directly or indirectly, after 48 hours in aureomycin concentration stronger than 1/100,000.

The blood aureomycin level varies in a reciprocal manner with the number of stools per day.[8] Harrell, Means et al.[9] obtained blood concentrations of 2 to 15 micrograms per c.c. with oral doses of 4 to 8 grams per day. Harrell and Heilman [10] found the concentration of aureomycin in bile to be eight to 16 times that of blood.

Harvey, Mirick and Schaub [11] observed 48 patients for toxic effects of aureomycin. Thirty-seven had examinations of blood and urine, thymol turbidity, cephalin flocculation and bromsulfalein tests, and serial electro-

TABLE II

Changes in Cephalin Flocculation Test after Routine Treatment of Amebiasis

	Before	Emetine	After	6 weeks after
1	Negative	12 grains	2 plus and 3 plus	Negative
2	Negative	5 grains	Negative	No data
3	Negative	12 grains	4 plus	Negative
4	Negative	12 grains	3 plus	3 plus
5	Negative	12 grains	3 plus	Negative
6	Negative	12 grains	Negative	Negative
7	No data	12 grains	2 plus	Negative
8	Negative	5 grains	Negative	Negative

cardiograms. No evidence of marrow, kidney, liver or myocardial damage was found in the 37 patients.

To date, 20 patients with proved amebiasis have received aureomycin at Veterans Administration Hospital, Lincoln. Symptoms prior to treatment included indigestion, vague abdominal discomfort, occasional diarrhea, fatigue and scattered arthralgias. Four had suggestive impairment of liver function.

Stool specimens were examined by warm stage technic and by iodine stain, the patients having been previously prepared with cholphenolate and phospho-soda (Fleet). Four patients had narrowing or deformity of cecum consistent with amebic typhlitis by x-ray.

Aureomycin was given orally in divided doses of 0.75 to 1.0 gm. every six hours for a total of eight to 28 gm. Side effects were minimal, and in no case was it necessary to discontinue medication.

Patients with diarrhea or abdominal pain were relieved within 72 hours. Several whose chief complaint had been arthralgia noted prompt relief of symptoms. Those with roentgenologic changes in the colon initially were

TABLE III

Amebiasis Cases Treated with Aureomycin

Age	Symptoms	Parasites	Aureomycin Dose (grams)	Side Effect	No. of Stool Exams.	Period of Observation
54	Back pain 3 months	*E. histolytica*-cysts	8	None	5	5 months
60	Back pain 1 year	*E. histolytica*-trophozoites	8	None	6	5 months
31	Irregular diarrhea 5 years	*E. histolytica*-precysts	8	None	7	5 months
29	Arthritis, right hip 6 weeks	*E. histolytica*-precysts	17.5	Giddiness	4	3 months
58	Intermittent diarrhea 30 years	*E. histolytica*-trophozoites	20	None	9	5 months
24	Vague abdominal discomfort 3 months	*E. histolytica*-trophozoites	14.75	None	6	5 months
33	Intermittent diarrhea 5 years	*E. histolytica*-trophozoites	20	Slight diarrhea	7	3 months
22	None referable to G.I. tract	*E. histolytica*-trophozoites	20	None	7	3 months
28	R.L.Q. pain 2 years	*E. histolytica*-precysts	20	None	6	3 months
24	None referable to G.I. tract	*E. histolytica*-precysts	20	None	8	5 months
52	Right abdominal pain 1 year	*E. histolytica*-trophozoites; *E. coli*-trophozoites	20	Slight nausea	6	3 months
*53	Vague abdominal pain 2 years	*E. histolytica*-precysts	20	Slight headache	12	5 months
25	None	*E. histolytica*-trophozoites	20	None	3	3 months
26	None	*E. histolytica*-trophozoites; *E. coli*-trophozoites	20	None	5	3 months
40	Intermittent abdominal pain 8 weeks	*E. histolytica*-precysts	12	None	2	1 month
†28	Intermittent R.L.Q. pain 3 years	*E. histolytica*; *E. coli*; Giardia	21	None	6	5 months
20	R.U.Q. pain 1 month	*E. histolytica*-trophozoites; *E. coli*-trophozoites	28	Giddiness	4	3 months
53	Diarrhea 1 month	*E. histolytica*-trophozoites	20	None	4	3 months
23	Diarrhea 2 months	*E. histolytica*-trophozoites	12	None	4	3 months
25	Vague abdominal pain 8 months	*E. histolytica*-cysts	12	None	4	3 months

* Stools positive at six weeks; second course of 28 gm. given; four stool series negative up to two months later.

† Stools positive at six weeks; second course of 12 gm. given; four stool series negative up to three months later.

reëxamined after six weeks, and disappearance of the cecal deformity was found.

After completion of aureomycin therapy, the stool specimens did not contain the macrophages, epithelial cells and cellular debris so commonly

seen after other treatment. Two patients complained of perianal itching four to six weeks after treatment, however.

All patients had negative stools at termination of therapy. Two had heavy infestations of trophozoites at their six-week check-up. Both were given a second course of aureomycin; further stool examinations were negative up to three months later. Eight patients in this series have been observed for five months; 12 others have been followed three months. It is believed that this period has been sufficiently long to eliminate the factor of symptomatic relief due to reduced secondary bowel inflammation, and to confirm the absence of parasites in the stool.

Many more cases must be observed over a longer period before the efficacy of aureomycin against *E. histolytica* infestations can be defined. In this series, aureomycin compared favorably with other amebacidal agents in relief of symptoms and prompt elimination of parasites from the stool. Recurrence rate was no greater than with other agents. It is considered a desirable agent for the treatment of amebiasis because of the absence of serious toxic action.

Summary

1. Treatment of amebiasis by a combination of emetine, carbarsone and the iodine containing oxyquinoline derivatives has a significant failure rate, and produces toxic symptoms which may be easily overlooked.

2. Of 140 cases so treated, there were 11.5 per cent recurrences.

3. Thirty-five patients had serial electrocardiograms while receiving emetine. Thirty-seven per cent had abnormal tracings after emetine, and in 8 per cent changes were persistent after six weeks.

4. Seven of eight patients had elevated cephalin flocculation tests after emetine and carbarsone. One was persistently elevated after six weeks.

5. Reports of inhibitory action of aureomycin on *Endamoeba histolytica* are reviewed.

6. Results following aureomycin treatment of 20 amebiasis cases at Veterans Administration Hospital, Lincoln, Nebraska, are described.

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RADICAL CURE OF RELAPSING VIVAX MALARIA WITH PENTAQUINE–QUININE: A CONTROLLED STUDY *

By Bernard Straus, M.D., and Joseph Gennis, M.D., *New York, N. Y.*

During the recent war, extensive investigations were undertaken in the study and cure of malaria. These studies at first were directed particularly toward finding a substitute for quinine, the supply of which had been cut off by the enemy. It was soon found that quinacrine (atabrine), which had been known since 1930 but not sufficiently appreciated because of improper dosage, was a more satisfactory drug than quinine both as a suppressive and as a treatment of the acute malaria attack.[1] Quinacrine, however, has no effect on the relapse rate. Its toxic manifestations are not significant. In this country chloroquine, a 4-amino-quinoline derivative, was developed and found to be a highly effective preparation. Its toxicity is minor and it has three times the efficacy of quinacrine.[2, 3] British investigators [4] developed paludrine, a synthetic biguanidine compound which is nontoxic and highly potent. Both chloroquine and paludrine are active suppressives in vivax and falciparum malaria and quickly terminate the acute attack. Both act as true prophylactics, completely preventing falciparum infections. They also effect radical cure of this type of malaria. Neither has any significant effect on the relapse rate in *Plasmodium vivax* malaria. With the development of these two new preparations, the therapy of the acute attack in *P. vivax* and *P. falciparum* infections has therefore ceased to be a major problem.

The notorious tendency of *P. vivax* malaria to relapse has been explained by the occurrence of a tissue or exoerythrocytic phase in the life cycle of the parasite in man and other mammals which is not susceptible to the action of these drugs. This tissue phase of *P. vivax* has recently been discovered and reported by Professor Shortt at the Fourth International Congresses on Tropical Medicine and Malaria. Radical cure of relapsing malaria involves the destruction of the tissue stages of the parasites. The magnitude of the problem presented by *P. vivax* malaria is indicated by approximate relapse rates for infections of Pacific origin of 80 per cent and those of Mediterranean origin of 30 per cent.[5] Median intervals to relapse following treatment with quinine, quinacrine and chloroquine are 24, 50, and 61 days,

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respectively.[6] Following treatment, the relapse rate is not significantly altered. Another study [7] with the Chesson (Pacific) strain disclosed that chloroquine and quinacrine cleared the blood stream of parasites in most of the cases more rapidly than did quinine. However, the relapse rate after treatment with all three drugs is about the same, 90 per cent or over. The latent period following therapy for 50 per cent of patients with quinine, quinacrine and chloroquine is 15, 34, and 64 days, respectively.

Progress in the eradication of the relapse and presumably in the eradication of the tissue phase of *P. vivax* malaria was suggested by the early work of Sinton and Bird [8] and Jarvis [9] with pamaquine (plasmochin) and quinine which, employed concurrently, reduced the relapse rate significantly. These observations, which had generally been ignored, largely because of the fear of pamaquine toxicity, were confirmed at a later date by Kelleher and Thompson,[10] Berliner,[11] and Most.[12] Pamaquine had previously been employed chiefly because of its ability to eradicate the gametocytes of *P. falciparum*. Quinine, when used concurrently with pamaquine, potentiates the action of the latter drug. Neither chloroquine nor paludrine has this synergistic effect.[13]

Employing dosage levels of 60 mg. of pamaquine naphthoate and 2 gm. of quinine sulfate daily for 14 days, Most et al.[12] found the relapse rate and total failure rate during 120 days of observation to be 4 and 11.1 per cent, respectively, without serious toxic manifestations. Berliner, et al.[11] found that pamaquine had a curative action in 10 attacks of sporozoite-induced Chesson strain vivax malaria when the drug was given at a high dosage of 60 to 90 mg. in conjunction with 2 gm. of quinine daily for 14 days. They concluded that curative effects observed by other workers at lower dosage are attributable to greater strain susceptibility, to administration of the drug at a later stage of the disease, or to a lesser density of underlying tissue infection. It was suggested that the stage of the disease, as well as the tissue parasite density, might in effect be related; that is, a lesser density of the underlying tissue phase of the disease may result from either a smaller sporozoite inoculum or a diminution of an initial high density of tissue parasites. Especially at higher dosage levels (above 60 mg.), pamaquine has a significant degree of toxicity, one sufficiently serious to limit its general use. The toxic manifestations include anorexia, epigastric pain, abdominal cramps, nausea, vomiting, diarrhea, cyanosis, and circulatory disturbances such as dyspnea and hypotension. There are T-wave changes in the electrocardiogram, methemoglobinemia, hemolytic anemia, headache, dizziness, psychosis and coma. Hemolytic phenomena are especially frequent in the colored races.

Because of this toxicity, 18 analogs of pamaquine of the 8-amino quinoline structure, among the thousands of drugs tested by the Board for Coördination of Malarial Studies, were given clinical trials by Alving.[14] Of these, pentaquine (SN 13,276) 6-methoxy-8-(5′-isopropylaminopentyl-

amino)-quinoline, was most effective. The chemical structure of pentaquine, as well as other antimalarial drugs considered in this study, is shown in figure 1. It is related to pamaquine and isopentaquine. These drugs differ from each other only in the aliphatic side chain substituent in the 8-position. At the therapeutic dose, the toxicity of pentaquine is qualitatively the same and quantitatively approximately one-half to three-quarters that of pamaquine in adults.[15] One symptom, acute syncope, due to postural hypotension, occasionally occurs with pentaquine [13] but has not been observed following pamaquine. As with pamaquine, quinine acts syner-

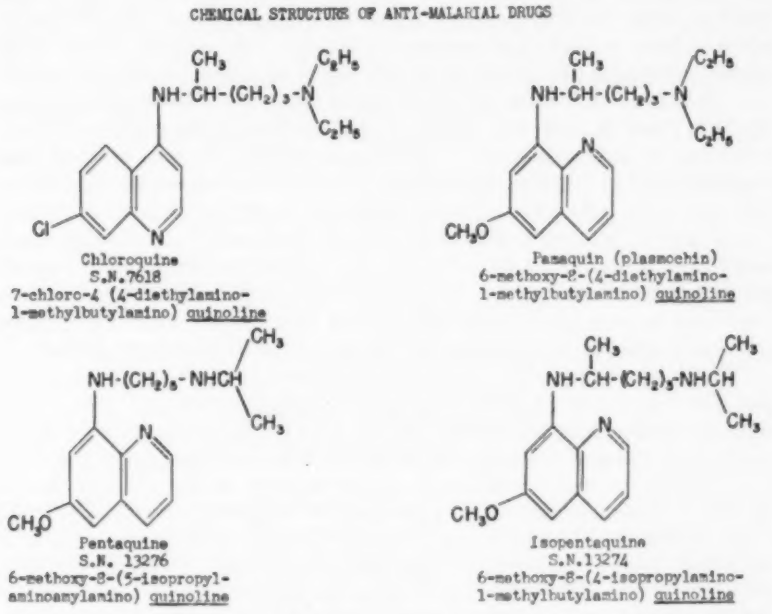

FIG. 1. Structural formulae of anti-malarial drugs showing similarity of configuration.

gistically with pentaquine. It is of interest that the group studied with the concurrent administration of quinine had less toxicity than the group treated without quinine.[16] Atchley, et al. showed that concurrent administration of quinacrine with pentaquine increased the toxicity of pentaquine.[17] It was shown [16] that, on an equal weight basis, pentaquine has greater curative activity and lower toxicity than pamaquine. In subjects with massive inoculations, which presented a severe challenge to the drug, it did not prevent relapses.[13] Later, another 8-amino quinoline derivative, isopentaquine,[18] was found to be slightly less toxic than pentaquine at high dosage levels. It became available too late to be included in this study.

Employing dosage levels of 60 mg. of pentaquine base with 2 gm. of quinine daily for two weeks, Alving [13] found that 60 mg. of pentaquine base have an effect on the relapse rate approaching that of 90 mg. of pamaquine base. However, 90 mg. of pamaquine produce severe toxic reactions, making it impractical for clinical use. Sixty mg. of pentaquine, on the other hand, caused toxicity similar to that produced by only 30 mg. of pamaquine, a dosage tolerated by most white patients. It was also suggested that pentaquine might prove clinically useful in doses less than 60 mg. a day. Although pamaquine must be given at 90 mg. of base to cure the severely infected non-immune individual, doses as low as 27 mg. of base a day were found to lower the relapse rate to a striking degree in returned service men who had been on prolonged suppressive therapy. By analogy, Alving suggested that pentaquine might be found useful in doses considerably lower than those required for the severely infected volunteers studied by his group. At doses lower than 60 mg., Alving et al. found negligible toxicity, but the possibility of acute hemolytic anemia was raised. It was believed that hospitalization throughout the treatment course for purposes of observation was necessary. They found that a daily dose of 60 mg. of pentaquine base and 2 gm. of quinine sulfate administered concurrently in divided doses every four hours for 14 days reduced the relapse rate in severely infected patients from 98 per cent to 18 per cent. In moderate infections, relapse rates were reduced from 67 per cent to 4 per cent. With massive infections, pentaquine-quinine failed to prevent relapses in the four subjects studied.

Toxic manifestations of pentaquine include occasional anorexia, abdominal discomfort or pain, and slight methemoglobinemia. The symptoms at dosage levels higher than 60 mg. of base are similar to those which result from the administration of pamaquine, and it was suggested that drug fever might be encountered in a certain number of instances.[15] Severe anemia was encountered in one white patient. Electrocardiograms revealed a diminution in the height of the T-waves in some or all of the leads. T_3 sometimes became inverted; in other cases, an inverted T_3 became upright. In only one instance was the T-wave amplitude reduced below normal height. Serial electrocardiograms in such cases showed a return to the normal configuration of the electrocardiogram after the course of treatment was completed.[13]

The present investigation was designed to test the efficacy of pentaquine when employed concurrently with quinine in the radical therapy of the naturally acquired *P. vivax* malaria infection in man. This represents the completion of a study of which a preliminary report was published elsewhere.[19]

Methods

All the patients studied were veterans of World War II who were hospitalized at the Veterans Administration Hospital, Bronx, New York.

Because of the progressive development of immunity or diminution of parasite density in the exoerythrocytic tissue phase, the relapse rate at the time of the initiation of this study was unpredictable. It was therefore decided to employ a control series. Chloroquine, (SN 7618) 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, was selected for the control series because it is a highly effective agent in the treatment of the immediate attack and has no significant effect on the relapse rate.

As is shown in chart 1, chloroquine diphosphate was administered in a dosage of 1 gm., followed in six hours by 0.5 gm. and by 0.5 gm. on the second and third days, for a total dose of 2.5 gm. This is equivalent to 0.6 gm. of chloroquine base as an initial dose and 0.3 gm. in subsequent doses. In all cases, clinical evidence of a malarial relapse was required as well as a positive smear for *P. vivax*. Patients were discharged after three negative smears.

Pentaquine was employed as a monophosphate in a daily dose of 30 mg. of pentaquine base, 10 mg. being given every eight hours concurrently with

CHART I

Chloroquine Group (Control)

1. Clinical evidence of malarial relapse
2. Positive smear for *P. vivax*
3. Therapy—chloroquine base—0.6 gm. (initial dose)
   0.3 gm. in 6 hours
   0.3 gm. 2nd day
   0.3 gm. 3rd day
   Total 1.5 gm.

   (Chloroquine diphosphate tablets used; 0.25 gm. equivalent of 0.15 gm. chloroquine base)
4. Discharge after three negative smears
5. Follow-up at monthly intervals. Examinations and smears

0.6 gm. of quinine sulfate (see chart 2). This regimen was maintained for 14 days. Pentaquine was given in one-half of the recommended daily dosage of 60 mg. of base in an attempt to reduce toxicity. This was feasible because there was reason to believe that either some degree of immunity had been developed by some of the veterans who would undergo therapy, or that some diminution of parasite density in the exoerythrocytic tissue phase had occurred. Here, too, clinical evidence of a malarial relapse was required as well as a positive smear for *P. vivax*. The pentaquine-treated cases were carefully observed with electrocardiograms before and after therapy. Complete blood counts and urine examinations were done twice weekly and, in colored patients, daily hemoglobin and urine examinations were performed for evidence of hemoglobinuria. Patients were discharged after three negative smears.

Beginning in January, 1947, and ending July 1, 1948, alternate cases were selected for either chloroquine or pentaquine therapy. All patients had proved vivax malaria. Colored patients were not excluded from pentaquine therapy. However, there was only one colored patient in the pentaquine

group. A total of 99 cases are included in this series. Forty-nine patients were treated with chloroquine. Fifty cases were treated with pentaquine and quinine. There were, in addition to these, nine cases treated with chloroquine who were dropped from consideration. Two were dropped for lack of follow-up. Four were excluded because treatment was given after

CHART II

Pentaquine Group

1. Clinical evidence of malarial relapse
2. Positive smear for *P. vivax*
3. Therapy—Pentaquine base 10 mg. / Quinine sulfate 0.6 gm. } 8 q h x 14 days
4. Laboratory Data—Electrocardiogram before and after therapy
   Complete blood count and urine examination twice weekly
   3 consecutive negative smears
   Colored races—daily hemoglobin
   daily urine examination for hemoglobinuria
5. Toxicity study

July 1, 1948, and the follow-up interval was too short. Two heroin addicts were dropped because they were found to be infected with *Plasmodium malariae*. One patient was dropped because he was found to have a *Plasmodium ovale* infection. Eight additional cases had been treated with pentaquine and quinine, but were dropped from consideration. Two of

CHART III

Comparison of Chloroquine and Pentaquine-quinine Treated Patients

	Chloroquine	Pentaquine
Average age of disease	24.5 mos.	23.0 mos.
Relapses prior to therapy	5.5	4.8
Area of infection—Pacific	45	49
—Other	4	1

these cases were dropped for lack of follow-up. Four were excluded because treatment began after July 1, 1948, and two were dropped because there was no laboratory confirmation of infection at the time of therapy.

The two groups were found on analysis to be comparable in all significant respects (see chart 3). The average age of the disease in the chloroquine

CHART IV

Analysis of Follow-up Studies

	Chloroquine	Pentaquine
Over 12 months	80%	66%
Over 6 months	90%	92%
Less than 6 months	10%	8%

series was found to be 24.5 months. The average age of the disease in the pentaquine series was found to be 23.0 months. The average number of relapses prior to therapy in the chloroquine series was 5.5. The average number of relapses in the pentaquine-quinine series was 4.8. Forty-five of

the 49 patients in the chloroquine series saw service in the Pacific area. Forty-nine of the 50 patients in the pentaquine series saw service in the Pacific area.

Follow-up studies (see chart 4) were made at approximately monthly intervals on all patients. These included history, physical examination, and a blood smear for malaria. In the chloroquine group, 80 per cent of patients have been followed for one year or more; 90 per cent of patients have been followed six months or more, and 10 per cent have been followed for less than six months. In the pentaquine group, 66 per cent have been followed for one year or more; 92 per cent have been followed for six months or more, and 8 per cent have been followed for less than six months. The longest follow-up has been 18 months.

Results

Of the 50 cases in the pentaquine group, only one patient relapsed during the follow-up period, for a relapse rate of 2 per cent. The interval to relapse in this particular case was 115 days. This patient saw service in

Chart V

Analysis of Data

Proved Relapses	Pentaquine-quinine	Chloroquine
No. of patients	1	17
Relapse per cent	2%	34.6%
No. of relapses	1	22
Four relapses	0	1
Two relapses	0	2
One relapse	1	14
Average interval to relapse	115 days	128 days

the Southwest Pacific area. In the chloroquine control group of 49 patients, there were relapses in 17 patients, for a relapse rate of 34.6 per cent. Fourteen of these patients saw service in the Southwest Pacific area and three saw service in Korea. There were 22 relapses in the 17 patients. One patient had four relapses, two patients suffered two relapses, and 14 patients had one relapse. Five of the patients in the chloroquine group were subsequently treated in a relapse with pentaquine and are also included in the pentaquine series. All other chloroquine relapses were treated subsequently with chloroquine. The average interval to relapse was 128 days (see chart 5). The shortest interval was 44 days and the longest interval, 395 days.

Toxicity

Toxic manifestations to pentaquine-quinine were minor. In no case was it necessary to discontinue pentaquine because of toxicity. In one case, quinine was discontinued because of cinchonism. Some toxic manifestations were observed in 75 per cent of patients. Most of these were insignificant (see chart 6). Nausea and anorexia were common during the first

four days. Vomiting would occasionally occur during this period. Mild abdominal pain was relatively frequent after the first week. Tinnitus, dizziness and headache were common. No frank hemolytic reactions were observed, but six patients showed a drop of one million red blood cells or less in the course of therapy. Drug fever varying from 99.6 to 103.4° F. developed in seven patients from the seventh to the eleventh day of therapy, and subsided spontaneously in one day without modification of treatment.

CHART VI

Toxicity to Pentaquine-quinine

	No. of Patients	Day of Therapy	%
Nausea	15	1–4	30
Abdominal pain	14	7–10	28
Dizziness	10	1–5	20
Tinnitus	9	2–14	18
Vomiting	9	1–4	18
Fever (99.6°–103.4°)	7	7–11	14
Anemia drop of 0.6–1.15 M. RBC	6	2–6	12
Headache	6	1–5	12

Sinus bradycardia was noted in two patients with no other cardiac or electrocardiographic abnormalities. Chloroquine toxicity was negligible. Two patients complained of pruritus. In no case was it necessary to discontinue chloroquine.

COMMENT

The shortest interval to relapse was 44 days, indicating that all the recorded relapses represent true relapses and not recrudescences of inadequately treated attacks, since it has been shown that short term relapses, i.e., those occurring within a month after treatment, are eliminated after adequate treatment.

The patient who relapsed to pentaquine was given two courses of atabrine at another hospital without eliminating the parasitemia. This would indicate that the patient had a heavy infestation with the parasite or a particularly resistant strain, and this may account for the failure with pentaquine.

The Pacific strain of *P. vivax* malaria is characterized by a much higher incidence of relapses. Consistent with this fact, all our patients who relapsed acquired their infection in the Pacific area.

During the last year of our study there was a sharp decline in the number of admissions for malaria. Since by July, 1947, most of the veterans had left the Pacific area some two years previously, this is consistent with the natural history of relapsing *P. vivax* malaria. It was in expectation of this diminution in malarial relapses that the need for a control series with chloroquine was considered essential.

During the course of follow-up study a significant number of the chloroquine-treated cases reported symptoms which they attributed to, and which

were suggestive of, malarial relapse. However, when these patients, contrary to instructions, failed to report or took atabrine or quinine without supervision or laboratory confirmation, these episodes were not included in the relapse rate figures. Hence it is likely that the reported relapse rate in the chloroquine group represents a minimum relapse rate.

It is also to be noted that our maximum follow-up period of 18 months is not adequate to include all relapses, since it is well known that relapses may occur for two to three years or longer following the primary attack.

It is our impression that in all probability some of the toxic manifestations were due either to the disease itself or to quinine. This especially is true of the anemia, since malaria itself is a hemolytic disease.

Conclusions

In the treatment of relapsing *P. vivax* malaria of World War II veterans, pentaquine administered concurrently with quinine in the indicated dosage has proved to be a highly effective curative agent. Toxic manifestations were insignificant at the dosage level employed.

Eradication of relapsing *P. vivax* malaria was achieved in 98 per cent of the patients treated with one-half of the previously recommended dosage of pentaquine.

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CLINICAL DISORDERS OF THE NEUROHYPOPHYSIS*

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DIABETES insipidus is the only clinical disorder generally conceded to be of neurohypophyseal origin, but accumulating evidence suggests that the neurohypophysis may have functions now scarcely appreciated. If such functions exist, they appear to be anti-adrenocortical in nature. The experimental data supporting such speculation are meager and largely unconfirmed, but a considerable body of clinical information can be interpreted in a corroborative manner. In view of the current emphasis upon hyperadrenocorticism in its various forms, it would seem important not to overlook the possible existence of antagonistic homeostatic mechanisms. The purpose of this paper is to suggest that we may now be entering the fourth phase of our knowledge concerning the physiology of the posterior pituitary gland.

The complicated controversies between those who believed diabetes insipidus to be of hypophyseal origin (phase 1) and those who championed the hypothalamic origin (phase 2) have been critically reviewed by Fisher and associates [1] in a monograph describing their own classic studies which did so much to reconcile these opposing views by establishing the supraoptico-hypophyseal tract as a functional antidiuretic unit (phase 3). Phase 4 seems to be that in which the adrenal cortex came into prominence as an opposing factor, and metabolic disturbances other than diabetes insipidus are therefore to be considered.

OBESITY

The principle of mutual antagonism between the adrenal cortex and the neurohypophysis finds support in studies which indicate that neuro-endocrine disease can produce qualitative metabolic changes promoting storage of fat without violating the fundamental thermodynamic principle that obesity means excess of caloric intake over caloric output. There seems to be no disagreement, for example, that the obesity in that type of Cushing's syndrome due to primary hyperadrenocorticism results at least in part from overproduction of corticoids which accelerate conversion of protein to glucose and which also suppress the rate of peripheral glucose oxidation.[2] The same situation is established if a normal subject is deprived of contra-adrenocortical hormone.

Two recent reviews [3, 4] present the altogether convincing evidence that hypothalamic lesions produce obesity chiefly by increasing consumption of food. Yet there are additional reasons for believing that such lesions also

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lead to changes in the metabolic mixtures of endocrine origin which accelerate conversion of glucose to fat. Heinbecker, White and Rolf [5] observed that canine obesity was most pronounced when the neurohypophysis had been so denervated as to include destruction of both paraventricular nuclei, a condition also reputed to be followed by degenerative changes in the anterior lobe basophils and atrophy of their respective target organs—the thyroid, the ovarian follicles and the sperm cells.[6, 7] Since in such a preparation the anterior lobe eosinophils are permitted to act in an unrestrained manner on the adrenal cortex and its respective target organs, and since simultaneous suppression of the basophil-thyroid-gonad complex predisposes to lethargy, hypometabolism and hypercholesterolemia, conditions favorable to storage of fat are thereby established. This state of *relative* corticoid excess may, therefore, explain why animals with hypothalamic hyperphagia convert carbohydrates to fatty acids at an accelerated rate.[8]

Diabetes Mellitus

However much difficulty one may have in defining diabetes mellitus with satisfaction, it seems certain that hyperfunction of the eosinophil-adrenocortical complex increases insulin-resistance, and vice versa. This concept is clear from clinical observations on acromegaly and the eponymic disorders of Addison, Simmonds and Cushing; it is also supported from the experimental side by the familiar ameliorating effects of hypophysectomy or adrenalectomy upon pancreatic diabetes and by the Young type of diabetes. Not so widely appreciated, however, are the demonstrations by several workers that the necessary endocrine derangements can be initiated by lesions in the hypothalamus.

Whereas it has long been known that lesions in the floor of the third ventricle can cause chronic hyperglycemia,[9, 10] no reasonable mechanistic explanation was offered until Heinbecker [11] showed that dogs whose neurohypophysis had been so denervated as to result in atrophy of the supraoptic and paraventricular nuclei exhibited not only degenerative changes in the anterior lobe basophils but eosinophilic predominance and increased resistance to insulin, mediated presumably by the unrestrained stimulating action of these eosinophils upon the adrenal cortex and their inhibitory effects on the islets of Langerhans. It would be extremely important to confirm these claims, for they mean that underactivity of the neurohypophysis sensitizes the organism to adrenocortical secretions and mimics the picture of primary hyperadrenocorticism save for the absence of excessive corticoid formation. Morgan [12] found atrophic paraventricular nuclei in each of 15 patients with diabetes mellitus so examined, and pituitary eosinophilic proliferation has previously been reported.[13, 14] These changes have not been observed by others,[15, 16] but no implication is here made that chronic hyperglycemia has only one origin.

Diabetes Insipidus

Although nearly total destruction of the supraoptic nuclei, with consequent atrophy of the neurohypophysis, is the essential lesion in experimental diabetes insipidus,[17] it is not the only factor, for the adrenal cortex must also be intact. Silvette and Britton [18] were apparently the first to suggest that the posterior pituitary and the adrenal cortex exert opposing actions upon the renal excretory rates of salt and water. The sometimes conflicting literature concerning the ameliorating effects of adrenalectomy upon experimental polyuria, the curiously delayed water diuresis of human subjects with diabetes insipidus, the production of polydipsia and polyuria by overdosage with doca, the opposing effects of pitressin and adrenocortical hormones on the renal excretion of electrolytes, the susceptibility of adrenalectomized animals to water intoxication, and the depressing action of excessive quantities of pituitrin on adrenocortical function have been reviewed elsewhere.[19] Since then, Birnie and coworkers [20] reported that the blood of adrenalectomized rats contains an increased amount of pitressin-like substance which disappears following hypophysectomy. Roemmelt, Sartorius and Pitts [21] showed that the renal tubules of adrenalectomized dogs excrete variable loads of salt and water in such a manner as to suggest that they are exposed to an excessive amount of antidiuretic hormone.

Although pituitrin and doca appear to exert opposing actions on the renal transport of sodium and water, no one would suppose that the combined action is that of simple chemical neutralization. Diabetes insipidus can be established, for example, either by pitressin-deficiency or by excess administration of doca, but this is due on the one hand to a lowered renal threshold for water with consequent primary polyuria, and to hypernatremia and consequent primary polydipsia on the other.[22] Nevertheless, the gross end result is that of physiologic antagonism. Peters [23] reported a case of a patient with acute postcraniotomy diabetes insipidus in whom a high blood sodium concentration developed because of water deprivation. This would suggest that the blood electrolyte pattern in diabetes insipidus might mirror that of Addison's disease if the patient with primary hypopitressinemia (diabetes insipidus) could be persuaded to drink less water. Each of these two diseases is characterized by a strikingly similar delay in renal excretion of a large water load, due possibly in diabetes insipidus to a relative predominance of doca-like steroids from the adrenal cortex, and in Addison's disease to uncompensated activity of the posterior pituitary. Whatever the intimate details of their hormone actions may be, the neurohypophysis and the adrenal cortex appear to counterbalance each other's overall influences upon the turnover of salt and water.

Gonadal Failure

There is a voluminous literature [24, 25] on the hypothalamic control of sexual functions, but the mechanisms are still obscure. It might be stated here

that either gonadal atrophy or gonadal hypertrophy apparently can result from lesions in either the hypothalamus or adrenal cortex, a circumstance which once again suggests the existence of contrahormone action between the two organs. Precocious puberty, for example, may be produced by any process which involves the production of excessive luteinizing hormone or androgenic steroids from the adrenal cortex or testis.[26] On the other hand, Seckel and coworkers [27] reviewed eight cases of the adrenogenital syndrome due to destructive lesions involving the tuber cinereum, in some of which the 17-ketosteroid output was normal, so that one is tempted to conclude that the excess of androgenic steroid was relative rather than absolute. As to conditions characterized by failure of this system, it can only be said here that luteinizing hormone probably originates in the pituitary eosinophils,[7] and that, therefore, corpus luteum and Leydig cell function might be expected to diminish relatively in conditions associated with basophilic hyperfunction. The follicle-stimulating hormone, on the other hand, is probably of basophilic origin, since denervation of the neurohypophysis, with its attending basophilic degeneration, is followed by atrophy of the seminiferous tubules and ovarian follicles as well as of the thyroid.[7] If so, it is understandable why waning of sexual power is so frequently associated with Cushing's syndrome, diabetes mellitus, obesity and hypertension. It has long been known that hypothalamic lesions can cause atrophy of germinal epithelium, and this is thought by some to be due to degeneration of certain trophic nerve fibers reaching the gonads in the sacral plexus. In support of this idea, Anderson and associates [28] reported a case of seminiferous tubule failure in a man with gliosis of the hypothalamus, although Dr. A. T. Rasmussen, who examined the pituitary, evidently thought the basophils were abnormal, since his report was quoted as follows: ". . . there are present many foamy cells, probably derived largely from basophils. Normal basophils are therefore reduced in number. . . . *Pars tuberalis* has many foamy cells. . . . The foamy cells are apparently late stages of Jan Mellgren's 'hypertrophic amphophiles' (Acta path. microbiol. Scandinav. Suppl. 60, 1945, pp. 1–77)." Heinbecker [29] regards Mellgren's amphophiles as hypofunctioning, degenerated basophils. No satisfactory theory has been advanced to explain how pineal tumors, for example, produce excessive amounts of FSH and enlarged testes, but it might be well to examine some such subjects for evidence of basophilic proliferation in the anterior pituitary.

Hypertension

Failure of many investigators to detect abnormal amounts of corticoids in the urine of hypertensive subjects does not rule out the possibility of *relative* hyperadrenocorticism as an important pathogenic factor in at least some varieties of this disease. Although it cannot be said that Heinbecker has reproduced an experimental disorder resembling essential hypertension, he [5, 6, 9] apparently has shown that destruction of the paraventricular nuclei

in dogs is followed by many of the features of Cushing's syndrome, and he has also found clinical cases with this disorder in which the only detectable endocrine abnormality was the Crooke basophil, associated with and probably caused by atrophy of the paraventricular nuclei. In both man and dog the basophils were reduced in number, and their structure suggested diminished function, a consequence interpreted as meaning that the neurohypophysis secretes a humoral substance necessary for the growth and maintenance of the anterior lobe basophils, since there are no known nerve fibers of importance connecting the two main lobes of the pituitary.

To the "hypopituitrinemia" and the loss of basophilic function are attributed (1) diminished thyrotropic and gonadotropic hormone formation for the thyroid, ovarian follicles and germ cell involute, and (2) increased sensitization to the pressor action of epinephrine, renin, doca and progesterone.

With basophils diminished in number and in vigor, the anterior lobe becomes predominantly eosinophilic and exerts an unrestrained influence on the adrenal cortex. The principal evidence that a state of relative hyperadrenocorticism ensues consists of the demonstration that these animals exhibited moderate hypertension, increased insulin resistance, obesity, hypercholesterolemia and lymphopenia.

It is possible, therefore, to explain the hypertensive state on a neurohormonal basis and to divide it into two broad categories, depending upon whether the excess of total pressor substance is *absolute* or *relative*. Examples of the former are rare but better understood. They include (1) pheochromocytoma (epinephrine), (2) acute renal affections, such as glomerulonephritis and pyelonephritis (renin), and (3) tumors of the adrenal cortex and ovary, pregnancy (steroids). All three types are thought capable of activating the eosinophil-adrenocortical complex in one way or another.

The second group is large and vague, but it may consist of individuals genetically predisposed to vascular disease in whom "pituitrin" deficit exists either because the hypothalamus is chronically inhibited by abnormally intense cerebrocortical activity or damaged by various organic lesions. If repetitive bouts of sympathomimetic hyperfunction, renal ischemia or pregnancy are superimposed upon this basic defect, the hypertensive process appears earlier and in an exaggerated form. If it be objected that no consistent histologic changes have been found in the pituitary, the same may be said for the islets of Langerhans in diabetes mellitus; in either case the secretory deficit may be entirely functional and of minimal intensity, for it usually takes half a lifetime for either disorder to reach a clinical threshold.

Hyperfunction of the Neurohypophysis

Although other investigators [30] have failed to draw any positive conclusions from studies on the effects of continued and excessive pituitrin administration, Heinbecker [31] noted pronounced basophilic proliferation in the ante-

rior pituitary of a man who died of untreated chronic thyrotoxicosis, and he induced similar but less pronounced changes in dogs by periodic administration of pituitrin. These observations complement his older one that denervation of the neurohypophysis is followed by a decrease in the number of basophils and atrophy of the thyroid and gonads, and they seem to identify the basophils as the source of thyrotropic and gonadotropic hormones. If the balance between these cells is disturbed in the direction of basophilic predominance, it might be expected that signs of adrenal insufficiency will appear in Graves' disease, for example, and Heinbecker's dogs did indeed show a tendency to hypocholesterolemia and an increase in the number of circulating lymphocytes. If these claims can be confirmed, they represent the first description of a clinical syndrome attributable to hyperfunction of the hypothalamic nuclei governing the secretory rate of the neurohypophysis.

Discussion

Some of the familiar disorders so common in later life—hypertension, obesity, diabetes mellitus, chronic polyuria, and gonadal failure—can be attributed in part to failure of secretory processes under hypothalamic control. They are also known to be associated with primary hyperadrenocorticism. Other conditions suspected of being due to perversions of steroid metabolism are arteriosclerosis, cancer, osteoporosis, muscular weakness and virilism. If these abnormalities are added together, the sum is something close to Cushing's syndrome, a disease also known to develop rarely from destructive lesions in the floor of the third ventricle. In a broad and probably nonspecific manner, pituitrin exerts some actions which are antagonistic to those of renin, doca and progesterone, so it may reasonably be suggested that the neurohypophysis exerts important anti-adrenocortical effects.[5, 6, 32] A preliminary report by Hume[33] indicates that extracts of the hypothalamus can modify the alarm reaction, and Harris and de Groot [34] found that lesions in the posterior hypothalamus influence the secretion of adrenocorticotropic hormone by way of the hypophyseal portal circulation. Conversely, excessive pituitrin formation apparently depresses the activity of the eosinophil-adrenocortical complex as in thyrotoxicosis, so that, if the fundamental observations are correct, Cushing's syndrome and Graves' disease are in a sense mirror images of each other. Many of the manifestations of the aging process may therefore be regarded as examples of subtotal Cushing's syndrome due to partial failure of a homeostatic mechanism involving the neurohypophysis and the adrenal cortex as the chief protagonists. If so, effective therapy is not unthinkable.

Conclusions

1. Pituitrin exerts some actions which may be broadly interpreted as anti-adrenocortical in nature.

2. Obesity, diabetes mellitus, diabetes insipidus, gonadal failure and hypertension may be of either hypothalamic or adrenocortical origin.

3. It is suggested, therefore, that Cushing's syndrome represents a complete breakdown of a homeostatic mechanism which exists between the neurohypophysis and the adrenal cortex, and that many important disorders associated with aging are incomplete variants of the same process.

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CONGENITAL DIFFUSE LIPOMATOSIS *

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Localized or unusual depositions of fat are classified as lipomatosis to distinguish them from the ordinary form of obesity. There have been few articles concerning them because of their lack of clinical importance. They cause little concern except from a cosmetic point of view or when they mechanically interfere with normal function because of an unfortunate situation.

The etiological factors may be classified as primary or secondary. The secondary type could include the following: (1) Diffuse symmetrical lipomatosis (Fetthals; adenolipomatosis) in which the unencapsulated mass has a predilection for the neck region. These are found in the area rich with lymph glands and although they may be asymptomatic they may be more characteristic of Dercum's syndrome. (2) Adiposis dolorosa, or Dercum's disease, the cardinal features of which are pain, asthenia, psychic manifestations accompanying the lipomas. This type is more frequent in the female. Exacerbations and remissions occur in this type. (3) Adipositas cerebralis consists of a group due to intracranial lesions or associated with deficient functioning of the pituitary. Froehlich's syndrome is typical of this group. (4) Lipomatosis of the pseudohypertrophic form of muscular dystrophy in which the adipose tissue invades between the muscle bundles. (5) Lipodystrophia progressiva, a rare condition of young female children, characterized by complete disappearance of subcutaneous fat and the development of psychoneurotic symptoms. (6) Nodular, circumscribed lipomatosis may be single or multiple and affect women more frequently than men.

Heredity has not previously been considered as an etiological factor. This study presents three separate families in which several members in each family showed the abnormality (figure 1). One family originated in Indiana, and the other two came from a desert county in Utah.

The age of onset in all three families was in the second decade. The forearms and thighs were the sites of onset. Here is found the greatest number and the largest lipomas. The lipomas are numerous in all members who have them. There are between 50 and 150 on the average. Only one patient of the group suffered clinically because of mechanical disturbances. One member of each family is presented in the case study, together with photographs of the arm involved and microscopic sections.

Treatment should be directed to the etiological factor, if this can be determined, as in the case of pituitary involvement. Treatment, however, is generally unsuccessful except where surgical removal is indicated either for cosmetic reasons or because of mechanical disturbances.

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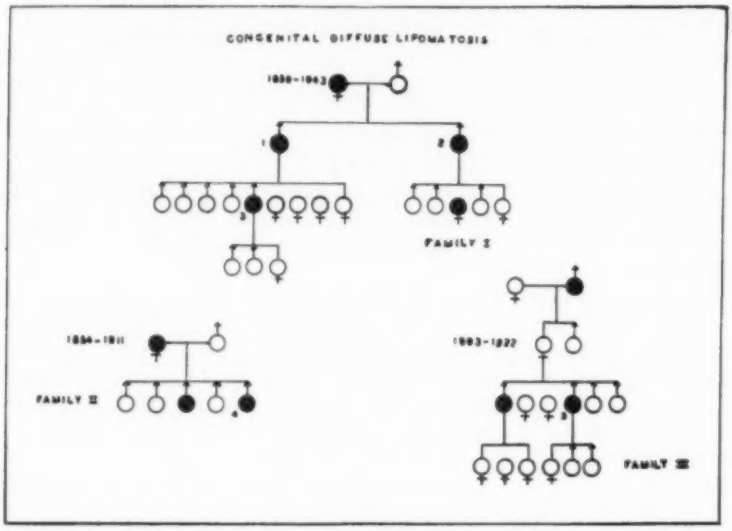


FIG. 1.

CASE REPORT

Case 1. This 64 year old white farmer's (figure 1, family 1, no. 1) chief complaint was a swollen left hand. The patient had had a previous cerebral vascular accident which had resulted in a left hemiplegia. His past history revealed an empyema in the right chest at 26 years of age, and typhoid fever during his childhood. The "fatty tumor" growth began at about 26 years of age. The masses were noted first on the forearms and thighs. In this area they became most numerous. He later noted some in the lumbar region.

The patient's mother also had had numerous fatty tumors. Photographs revealed the masses also in the neck. The patient's brother, son and one niece also had them.

On physical examination it was noted that the patient was generally obese. His gait was that of a hemiplegic patient. His speech was not well enunciated. There were numerous lipomas on the forearms and thighs, as well as some on the arms and in the lumbar areas. They were discrete, fairly firm and freely movable (figure 2).

The patient weighed 193 pounds and was 56.5 inches tall. The blood pressure was 140 mm. Hg systolic and 84 mm. diastolic. The pulse was 82 and the temperature 98.2° F.

The serological test for syphilis was negative. The hemoglobin was 86 per cent, the red blood cells numbered 4,420,000, and the white blood count was 10,200. The urine showed a specific gravity of 1.013, acid reaction, and was negative for albumin and sugar.

Biopsy of a tumor of the forearm revealed a yellow mass which measured 1.5 by 1 cm. in size. It grossly resembled a lipoma.

Microscopic sections presented a tissue made up of fat cells which were adult in type. They were well formed, without evidence of abnormality.

Pathological diagnosis: Lipoma.

Clinical diagnosis: Congenital diffuse lipomatosis.

Case 2. This 51 year old white male (figure 1, family 1, no. 2), a county employee, did not seek medical attention but coöperated with the study. He had no complaints except the presence of "lumps on the arms" and excessive perspiration. The patient first noted the "lumps on the arms" when he was 18 years of age. Since the onset they had become progressively larger and more numerous. They were more numerous on the forearms and thighs and he had several below the xiphoid process and costal margins. The left arm was more involved than the right.

The patient weighed 176 pounds and was 65.5 inches tall. His blood pressure was 140 mm. Hg systolic and 80 mm. diastolic. The pulse was 76 and the temperature 98.4° F. The serological test for syphilis was negative. The hemoglobin was 98 per cent, the red blood cells numbered 5,010,000, and the white blood count was 7,500.

The urinalysis showed a specific gravity of 1.018, acid reaction, and was negative for albumin and sugar. Figures 3 and 4 show the lipomas of the forearms.

Diagnosis: Congenital diffuse lipomatosis.

FIG. 2.

Case 3. This 30 year old railroad brakeman's (figure 1, family 1, no. 3) chief complaint was "gas in the abdomen." His symptoms were referable to a hyperacidity noted after a gastric analysis.

Physical examination revealed a thin white male with one lipoma on the right side of the neck and one on the left forearm. The throat was injected. The heart measured 7 cm. to the left of the midsternal line and 3 cm. to the right in the fifth interspace.

The patient weighed 124 pounds. His blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. The pulse was 60, and the temperature 98° F.

The serological test for syphilis was negative. The blood count was normal. The urinalysis showed no abnormality.

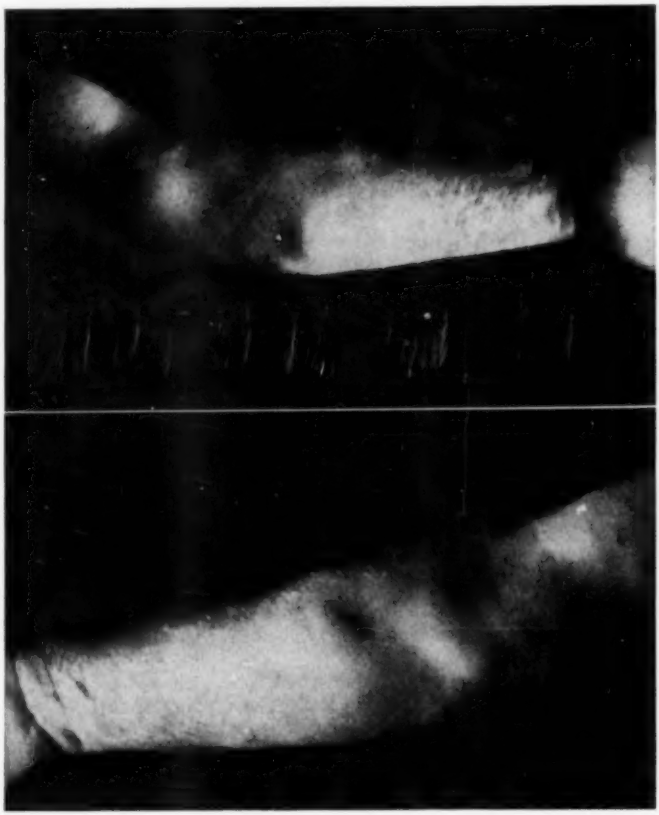
The diagnosis of congenital diffuse lipomatosis was made.

Case 4. This 56 year old male (figure 1, family 2, no. 4) had had a cerebral vascular accident two years before the present examination. The patient stated he first developed the lipomas on the forearms at the age of 26 years. Later they were noted on the thighs and the most recent had appeared in the area of the costal margin. They

had increased in number and size. The lipomas of the forearms are noted in figures 5 and 6.

Physical examination revealed an emotionally unstable white male. Loss of vision in the right eye was noted. There was a right-sided hemiplegia. The weight was 151 pounds. The blood pressure was 234 mm. Hg systolic and 130 mm. diastolic. The pulse was 80, and the temperature 98.4° F.

Examination of the urine showed a specific gravity of 1.014. There was a slight trace of albumin and a negative test for sugar. The serological test for syphilis was negative. The blood count was normal.



FIGS. 3 and 4.

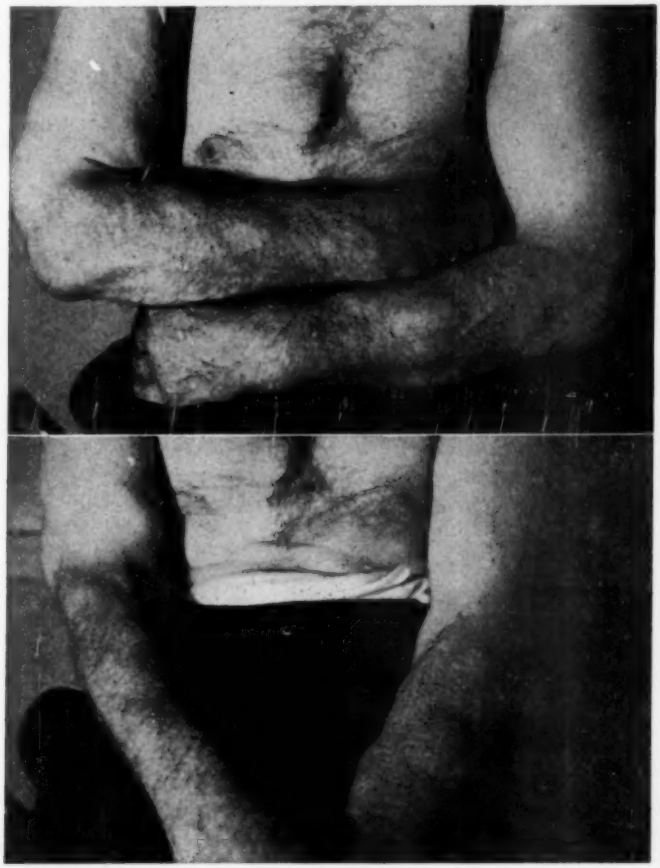
A mass removed from the forearm consisted of a lobulated lipoma which measured 4 by 2.7 by 1.2 cm. It was thinly encapsulated and the cut surface presented the typical yellow fat appearance of this type of tumor.

Microscopic sections presented a benign lipoma which was made up of adult fat cells. There was some peripheral fibrosis.

Pathological diagnosis: Lipoma.

Clinical diagnosis: Congenital diffuse lipomatosis.

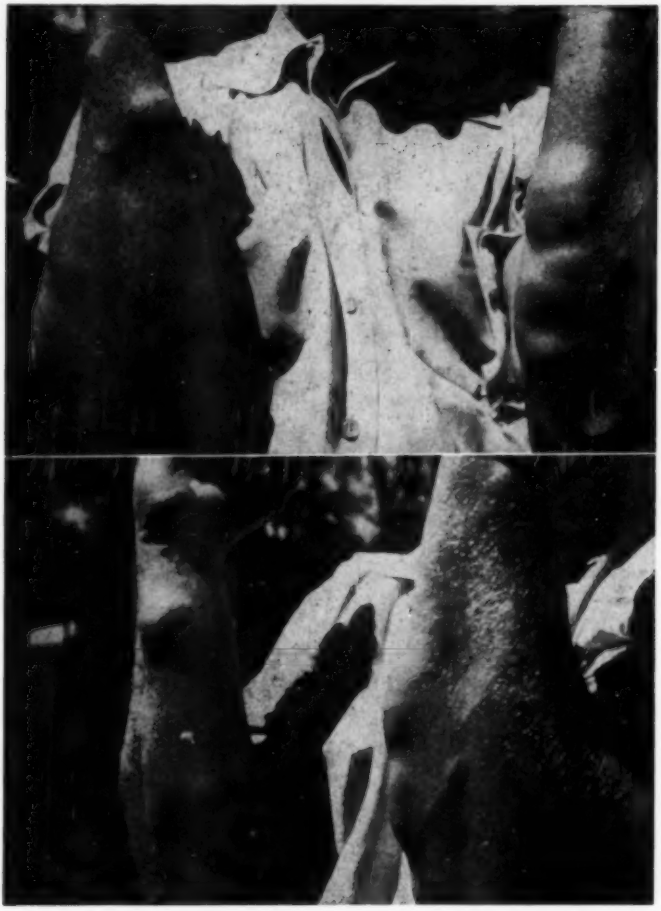
Case 5. The chief complaint of this 28 year old mason's helper employed by a smelting company was "masses on the arms and legs." The patient first noted the



FIGS. 5 and 6.

masses at 18 years of age. A few days before another lipoma appeared the patient noted "soreness deep in the tissues." A few days later the small mass was felt and rapid growth was noted. The masses were neither tender nor discrete. The patient had counted 78 lipomas which varied from 10 cm. to 0.5 cm. in size (figures 7, 8, 9, 10).

Physical examination revealed a slightly obese white male with numerous lipomas on the arms (figures 7, 8) and thighs (figures 9, 10). His weight was 178 pounds and he was 55.5 inches tall. The blood pressure was 126 mm. Hg systolic and 80 mm. diastolic. The temperature was 98.4° F. and the pulse 80.

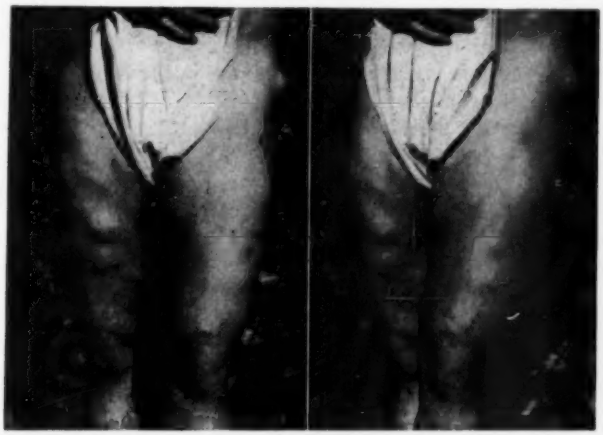


FIGS. 7 and 8.

The serological test for syphilis was negative. The blood count was normal, as was the urinalysis. The lipomas were removed in two stages and the following pathological reports obtained:

June 18, 1945. The specimen consisted of a large number of lipomas. There were approximately 30 in number, although some of the smaller masses might be part of

the larger masses. The largest piece measured 7 by 6 by 2 cm. Microscopic sections presented a simple lipoma. The structures were well formed and no undue fibrosis was present. The structures throughout were quite well defined. Pathological diagnosis: Lipomas, non-malignant.



FIGS. 9 and 10.

June 26, 1945. The specimen consisted of 29 lipomatous masses which measured up to 5.5 by 4 by 3 cm. in size. They were all thinly encapsulated. They all had the same general appearance. Microscopic sections presented fatty tissue. The cells were full and plump. The membrane was thin and there was nothing suggestive of malignancy. Pathological diagnosis: Multiple lipomas. Clinical diagnosis: Congenital diffuse lipomatosis.

CONCLUSIONS

1. Three family trees of subjects showing congenital diffuse lipomatosis are presented.
2. To the usual classification of the lipomas a new type is added, congenital diffuse lipomatosis.
3. Five cases along with the photographs are presented.
4. Both sexes have the abnormality and transmit it.
5. The thighs and the forearms are the sites of the first and most numerous lesions.

PERNICIOUS ANEMIA IN THE AMERICAN NEGRO *

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Pernicious anemia is considered to be rare in the Negro race. In 1943 Schwartz and Gore [1] compiled only 106 cases [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17] from the literature but added 93 cases of their own. They reviewed 1,000 consecutive diagnoses of pernicious anemia made at the Cook County Hospital between 1931 and 1942 and found that 93 of the patients were Negroes. According to the same authors, the largest series previously recorded from one institution had been 33 cases from the Johns Hopkins Hospital, reported by Wintrobe [2] in 1942. Prior to 1942, no group larger than 14 [3] had been recorded. One additional case in a Negress was described by Hardgrove et al. [18] in 1944. It is the purpose of the present communication to review the individual data on 15 Negro patients with pernicious anemia admitted to the University of Virginia Hospital in the years 1933 to 1947, inclusive, and to compare the incidence, symptomatology and response to liver treatment in this group with similar observations made on 115 white patients admitted during the same period.

The criteria for a diagnosis of pernicious anemia were:

1. Macrocytic anemia.
2. Achlorhydria after histamine.
3. Symptoms suggestive of pernicious anemia.
4. Absence of other demonstrable causes for macrocytic anemia.
5. Megaloblastic type of erythrocytopoiesis when sternal marrow studies were performed before treatment was instituted.

To evaluate response to treatment with liver extract, both the reticulocyte response and the rise in erythrocyte counts were considered. Rise in red blood count of 0.4 million per week was assumed to be optimal. A response of this degree or better was graded 4 plus; 0.3 million was graded 3 plus; 0.2 million was graded 2 plus; 0.1 million was graded 1 plus; and less than this, zero. Counts obtained during the two to eight weeks' period following institution of therapy were averaged to obtain the weekly response. The maximal expected reticulocyte response was calculated from the formula $R = (82 - 22E)/(1 + 0.5E)$, where R = reticulocyte response and E = red cell count before treatment.[19] The response was expressed in per cent of the calculated maximum.

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The individual data on the 15 Negro cases are presented in table 1. Five of these were diagnosed in the first 10 years of the study period and 10 in the last four years. It will be seen that the ages of the patients ranged from 31 to 81 and that there were twice as many males as females. Glossitis was recorded in seven instances but was noted as absent in six. Neurologic

TABLE I

Data on 15 Patients with Pernicious Anemia

CASE NUMBER	YEAR DIAGNOSED	AGE (YRS.)	SEX	GLOSSITIS	CNS INVOLVEMENT	WEIGHT LOSS (LBS.)	INITIAL R.B.C. (MIL.)	INITIAL HEMOGLOBIN (GMS.)	ICTERUS INDEX	MEAN CORPUSCULAR VOL. (CU. MICRONS)	MEAN CORPUSCULAR HEMOGLOBIN (MICRO MICRO GRAMS)	MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION (PERCENT)	STERNAL MARROW	RETICULOCYTE RESPONSE (% OF EXPECTED MAXIMUM)	R.B.C. RESPONSE (MILLION / WEEK)
1	1934	52	M	2+	2+	—	3.66	9.5	3.0	110.0	26.4	33.6	—	—	—
2	1935	40	F	2+	0	—	1.50	8.2	—	—	—	—	—	58	.5
3	1935	46	F	—	0	—	2.60	7.8	9.3	119.0	31.6	26.6	—	87	0
4	1945	65	M	3+	3+	—	1.50	6.0	8.0	133.3	40.0	30.0	MEG	50	.1
5	1944	60	M	0	0	20	0.99	3.5	17.0	111.0	34.3	31.9	MEG	79	.93
6*	1944	81	M	0	0	—	—	—	—	—	—	—	—	—	—
7	1944	67	M	0	0	20	1.92	7.5	11.0	129.0	39.1	31.3	MEG	61	.7
8	1944	81	M	2+	0	30	0.70	2.4	9.2	143.0	34.6	24.2	MEG	41	—
9	1944	55	F	3+	0	25	2.30	8.5	12.0	120.0	41.8	31.8	MEG	52	.1
10	1947	84	M	1+	0	20	2.80	11.0	7.0	121.4	39.5	32.5	MEG	17	.3
11	1946	56	F	0	0	50	1.00	—	20.0	118.5	38.8	32.9	MEG	40	.1
12	1942	52	M	—	2+	30	1.54	6.3	—	130.6	40.9	31.3	MEG	2	—
13	1941	31	M	0	3+	30	1.34	4.5	13.0	105.0	33.5	32.2	—	70	.5
14	1944	65	F	3+	3+	30	2.00	8.0	13.0	117.0	45.0	37.6	MEG	48	.3
15	1945	77	M	0	1+	—	1.16	5.0	4.0	108.0	43.3	—	—	—	—

MEG = MEGALOBLASTIC

* SEEN IN CLINIC. TREATED BY LOCAL PHYSICIAN AND LATER ADMITTED FOR OPERATION INCLUDED IN SERIES, BUT NOT IN AVERAGE RESPONSE.

signs or symptoms were found in six of 14 cases. Weight loss from 20 to 50 pounds was recorded in nine of the 15 case histories, but no mention of weight change was made in six instances. The initial red blood count was under two million in nine and was higher than this figure in five. Six initial icterus indices were under 10 and six above. The maximum reticulocyte re-

sponse to liver therapy varied from 2 per cent of the expected maximum to 79 per cent. Seven of the patients had a maximum reticulocyte response greater than 50 per cent of the expected maximum, and five had less than 50 per cent. The response in four patients could not be evaluated because of in-

TABLE II

Comparison of Racial Incidence of Pernicious Anemia in University of Virginia Hospital (1933–1947)

	Negro	White
Total admissions	22,674	124,562
Percentage of hospital admissions	15.4	84.6
Total diagnoses of pernicious anemia	15	115
Incidence of pernicious anemia (per 100,000 adm.)	66	92
Percentage of p.a. which were females	33.3	59.1
Average age of patients with p.a. (yrs.)	57	60.7

sufficient data. The red cell response to liver therapy was optimal in four and suboptimal in six. The response could not be graded in five patients because the degree of anemia was not sufficiently marked to make data accurate.

TABLE III

Comparison of Symptomatology in Patients with Pernicious Anemia

	Negro	White
Incidence of glossitis in 13 Negroes and 112 whites (per cent)	53.9	56.3
Average weight loss in 9 Negroes and 71 whites (pounds)	28.3	18.7
Incidence of CNS involvement in 15 Negroes and 111 whites (per cent)	40.0	48.8
Average initial R.B.C. in 14 Negroes and 109 whites (millions)	1.81	2.21
Average initial hemoglobin in 13 Negroes and 109 whites (grams)	6.8	8.2

To compare pernicious anemia in the Negro with the disease in the white, the 115 cases occurring in whites in the same period were analyzed and these two groups were compared with regard to incidence, symptomatology and response to liver therapy.

TABLE IV

Response to Liver Therapy in Patients with Pernicious Anemia

		Negro	White
Average reticulocyte response in 12 Negroes and 38 whites (per cent of expected maximum)		46.8	66.5
	Grade		
R.B.C. response in 10 Negroes and 45 whites (number of patients)	4+	4	44
	3+	2	1
	2+	0	
	1+	3	
	0	1	

Racial Incidence (*Table 2*). The predominance of 115 white cases to 15 Negro cases is less striking when the ratio of 85.6 per cent white hospital admissions to 15.4 per cent Negroes is considered. When adjusted on this basis, the incidence of pernicious anemia is 92 cases per 100,000 white admissions to 66 per 100,000 Negro admissions. The average age of the colored group was slightly less than that of the white.

Racial Symptomatology (*Table 3*). While the incidence of atrophic glossitis and central nervous system involvement was the same in the two racial groups in our series, the Negroes had lost more weight and were more severely anemic than the white patients.

Response to Liver Therapy (*Table* 4). In comparing the response to liver therapy, a greater red cell response per week might have been expected in the Negro cases since they were more anemic, but in nine colored patients the weekly erythrocyte rise was 370,000, as compared to 570,000 in 45 white patients. The average reticulocyte response in 12 Negroes was only 46.8 per cent of the maximum expected, whereas in 38 white patients it was 66.5 per cent. Only four of 10 Negroes had an optimal rise in erythrocyte level following institution of liver therapy, compared to 44 of 45 white patients. In all individuals treated for an extended period of time, both the red blood count and hemoglobin eventually returned to normal values.

Discussion

Obviously the present series of cases is too small to allow any conclusions to be drawn. Even when combined with the 199 Negro cases of pernicious anemia previously reported, experience with pernicious anemia in Negroes is limited. The present report brings to more than 200 the cases recorded in medical literature.

It is almost impossible to establish complete racial purity in the modern American Negro. Although many of the present series presented pure Negroid characteristics, it cannot be established that there had been no admixture of white blood. The same comment can be made of the other reported groups. The accuracy of the teaching that "pernicious anemia never occurs in the full-blooded Negro" is entirely of academic interest. For practical purposes, it can be said that Negroes of apparently pure racial stock do develop pernicious anemia. It may be significant that 10 of the 15 cases in this series have been diagnosed in four years following the publications of Wintrobe [2] and Schwartz and Gore.[1] It appears likely that, as physicians discard the old belief that Negroid characteristics exclude the diagnosis of pernicious anemia, the disease will be recognized almost as frequently in the colored race as in the white.

Previous reports do not agree on the comparison of pernicious anemia in whites and Negroes. Swartz and Gore [1] found no difference in the two races. Kampmeier and Cameron [3] reported a higher incidence of neurologic involvement in Negroes, and Wilson and Evans [4] considered the disease less severe in Negroes. In this series there was no appreciable difference in the incidence or severity of glossitis and central nervous system involvement. Since the Negro group was more anemic at the time of admission, it appears probable that the greater weight loss in this group was a result of the longer duration of the disease and the associated anorexia.

Although the present series is small, the results suggest that response to antianemic principle in Negroes was definitely less marked than that of the whites. Both received parenteral injections of similar amounts of liver extract, and several subjects treated early in the period of study also received raw liver by mouth. It is well known that in patients with pernicious anemia, infections, generalized arteriosclerosis, severe liver disease and advanced neurologic involvement may inhibit the therapeutic response to liver extract. None of these four factors explains the difference observed in the two groups in this study. In one Negro (Case 4) it appears probable that the poor red cell response was due to an unsuspected appendiceal abscess that was demonstrated at autopsy. That malnutrition may have influenced the response to specific therapy is suggested by the greater weight loss in the Negroes before admission and by the fact that the hemoglobin and erythrocyte values eventually reached normal in all patients treated for an extended period. However, the nutritional state of the patient may be of little importance in response to therapy. One white patient with extreme emaciation, signs of multiple vitamin deficiency, and a serum protein of 3.6 gm. per cent had an optimal response to specific liver therapy. Another white patient with pernicious anemia developed diarrhea and lesions of the skin typical of pellagra during a period when the erythrocyte count was maintained at a normal level by concentrated liver extract intramuscularly. The pellagra disappeared on treatment with brewer's yeast. Since it is difficult to evaluate the influence of the nutritional state on the response to specific therapy, some racial factor must be considered as a possible explanation of the apparently inferior response observed in this group of Negroes. A careful study of a larger group of patients to determine if there is a difference in therapeutic response in the two races would appear worthwhile.

Summary

1. Individual data on 15 Negro patients with pernicious anemia are presented and a comparison is made between the incidence, symptomatology and response to liver therapy of this group and a similar group of 115 white patients with pernicious anemia.

2. The incidence of pernicious anemia was 66 per 100,000 Negro hospital admissions and 92 per 100,000 white hospital admissions.

3. As the diagnosis of pernicious anemia is considered more frequently in Negroes, the incidence will probably approach that recorded in the white race.

4. There was no significant difference in the symptomatology of the disease in the two races.

5. The response to specific treatment observed in Negroes was inferior to that which occurred in white patients. The possible explanations of this difference are discussed.

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DIATRIN, A NEW ANTIHISTAMINIC WITH MINIMAL SIDE REACTIONS *

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ALMOST every physician in his daily practice meets some variety of allergic manifestation which requires relief or palliation. Of late, the antihistaminic drugs have come into prominence because of their ability to alleviate this condition. Unfortunately, the unpleasant side reactions which frequently accompany their use sometimes necessitate their discontinuance. Investigations therefore continue for a more effective and less toxic antagonist to histamine which would demonstrate fewer side reactions.

The writer had the opportunity to procure one of the newer antihistaminics, Diatrin Hydrochloride,† for investigation. It was felt that, to evaluate clinically its therapeutic effectiveness and possible side reactions, more accurate results could be obtained with private than with clinic patients, since the former adhere more strictly to scheduled office visits. Only ambulatory cases were chosen. In the study, each patient was maintained on an antihistaminic drug for a period of one week and was then transferred to another one. Patients were instructed to make note of any reactions, beneficial or otherwise, for the period between office visits, i.e., 48 hours. If the side effects were too great (drowsiness, nausea, headache, etc.), the medication was stopped after 48 hours. Following a respite of a few days' duration, the patient was placed on another antihistaminic. In the uncomplicated cases, after each series was completed, medication was discontinued for a few days and a new series was begun. The study was made during the pollinating season (grasses, trees, ragweed).

The chemical formula for this new synthetic antihistaminic compound is N,N-dimethyl-N′-phenyl-N′-(2-thienylmethyl)-ethylenediamine monohydrochloride. The dosage administered was 50 mg. three times daily. Larger doses of Diatrin might have been given with a fair degree of impunity for the toxicity of the drug seems to be extremely low. Combes,[1] in his report on the toxicity of Diatrin, indicated that he administered daily to patients dosages varying from 100 to 1,000 mg. with practically no toxic effect.

In a comprehensive analysis of the treatment of 113 patients with Diatrin, only 13, or 11.5 per cent, showed any side effects, and these were of a fairly minor nature.

Before proceeding with the clinical evaluation of Diatrin, a brief review of some of the by-effects resulting from the earlier drugs is in order. It was in 1910 that Dale and Laidlaw [2] first reported the similarity of the effect of histamine and anaphylactic shock. Experiments to uncover compounds

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† Diatrin Hydrochloride was supplied through the courtesy of William R. Warner & Co., Inc., New York, St. Louis.

with histamine-inhibiting properties progressed rather slowly until 1937. In that year, Bovet and Staub [3] found two chemical compounds (thymoxyethyldiethylamine and N-phenyl-N-ethyl-N-diethylethylenediamine) which possessed antihistaminic and antianaphylactic properties. These phenolic ethers were too toxic to use clinically. In 1942, Halpern,[4] in France, announced the clinical effectiveness of a new compound, Antergan. Antergan gave fair results but was somewhat toxic. More recently, in 1944, Bovet and his associates [5] reported that a new compound (Neoantergan) was even more potent and less toxic. A Swiss histamine antagonist known as Antistine has also been shown to give benefit in some forms of allergy. Side effects have been noticed in some patients.[6] Although these drugs have given fairly good results in achieving symptomatic relief, we in this country have intensified our efforts to find a more effective and less toxic compound with antihistaminic activity. As a result of this research, some newer compounds (Pyribenzamine and Benadryl) have been made available clinically. Different degrees of sedation and other untoward side reactions have also been reported as a fairly common occurrence following these drugs. Feinberg [7] states that "Benadryl produces the most marked sedation, Antistine the least while the other drugs are intermediate in this action. The sleepiness from Benadryl may be so intense that the patient may be unable to be on his feet." Dizziness, nervousness, tightness in the chest, dysuria, dryness of the mouth and nose, fall in blood pressure, and nausea and vomiting have all been noted. Benadryl, particularly because of its narcotic side reactions, may present a serious hazard. Slater and Francis [8] report an accident of this nature and suggest that care should be taken when administering the drug to persons operating automobiles or operating equipment or machinery. A case of granulocytopenia probably due to Pyribenzamine was reported by Blanton and Owens.[9] Disorientation,[10] epileptiform movements [11] and collapse [12] have also been reported. Lockey,[13] in a study of 28 cases of acute urticaria, had to discontinue the use of Benadryl in four cases because of the appearance of extremely severe reactions consisting of nausea, dizziness, blurring of vision and extreme drowsiness. Arbesman [14] in a study of 800 patients, reported that "44 or 5.5 per cent had to stop the drug because of the severity of the side effects. There were 218 patients who had a total of 374 untoward reactions."

Loveless,[15] in her survey of 26 clinical reports, stated that the most common side effects with Pyribenzamine were nausea, anorexia, heartburn, abdominal cramps, and occasionally vomiting and diarrhea. Twenty-three per cent of 1,905 individuals given Pyribenzamine developed undesirable side reactions. The comparable figure for 655 trials with Benadryl was 61 per cent.

Tuft [16] has stated that "the great disadvantage of both of these drugs is their side-effects, these never are serious but sometimes are sufficiently dis-

TABLE I

Total Number of Patients Treated:

Diatrin..... 56
Benadryl..... 55
PBZ..... 54

Hay Fever

Preparation	No. of Cases	No. of Cases Improved	% of Cases Improved
Diatrin	30	22	73.3
Benadryl	30	28	93.3
PBZ	30	28	93.3

Urticaria

Preparation	No. of Cases	No. of Cases Improved	% of Cases Improved
Diatrin	9	8	88.9
Benadryl	8	6	75
PBZ	7	7	100

Allergic Rhinitis (Vasomotor Rhinitis)

Preparation	No. of Cases	No. of Cases Improved	% of Cases Improved
Diatrin	10	3	30
Benadryl	10	3	30
PBZ	10	4	40

Miscellaneous
(Contact Dermatitis, Allergic Dermatitis, Vernal Conjunctivitis)

Preparation	No. of Cases	No. of Cases Improved	% of Cases Improved
Diatrin	7	1	14.3
Benadryl	7	0	0
PBZ	7	1	14.3

Side Effects

Type	Diatrin	Benadryl	PBZ
Drowsiness	3	41	29
Nausea	2		1
Vomiting			
Abdominal cramps	1		
Palpitation	1	1	
Groggy	1		
Foggy		1	
Jittery	1	1	
Tight feeling in chest	1	1	1
Running nose	1	1	
Headache		1	5
Generalized urticaria		1	
Itchy eyes			1

Total Number of Cases with Side Effects:

Diatrin..... 7 (12.5%)
Benadryl..... 46 (83.6%)
PBZ..... 34 (62.9%)

comforting to necessitate withdrawal . . . the most frequent and important side-effect is drowsiness, which seems more frequent from Benadryl than from Pyribenzamine."

In the preliminary investigation on Diatrin, 27 cases were studied—12 cases of pollinosis, five cases of allergic rhinitis, two cases of urticaria, one of food allergy, two each of vasomotor rhinitis and contact dermatitis, and three of vernal conjunctivitis. Of these 27, 15 obtained symptomatic relief and only three complained of any side reactions (drowsiness (two) and urinary frequency).

In a continuing and supplementary study, observations on the effectiveness of Diatrin on pollinosis (hay fever) were made. Of a total number of 30 cases, 25, or 83 per cent, showed improvement and relief and only three cases, or 10 per cent, demonstrated any side effects. The side reactions presented were nausea in one, nausea and vomiting in another, and indigestion in a third. The usual bad taste generally attributed to most antihistaminic compounds may have accounted for all three reactions. Two of these cases had some degree of relief despite their discomfort. At this writing, however, the bitter taste of Diatrin has been nullified by a light sugar coating. The masking of the nauseating taste of the pill may further reduce the incidence of some of the side reactions.

In a comparative study of Diatrin, Pyribenzamine and Benadryl, the total number of patients treated with Diatrin was 56, Pyribenzamine, 54, and Benadryl, 55. Only seven patients (12.5 per cent) exhibited side effects with Diatrin, whereas with Pyribenzamine 34 (or 62.9 per cent) and with Benadryl 46 (or 83.6 per cent) demonstrated side reactions. Each patient studied received 50 mg. three times a day over the same length of time. The resultant comparative analysis was then tabulated (table 1). Despite the bitter taste of Diatrin (which has been eliminated), patients preferred it to Pyribenzamine and Benadryl, probably because of its lack of side effects. Drowsiness was encountered in 29 cases using Pyribenzamine, 41 cases using Benadryl, and in only three cases with Diatrin.

In summarizing the results of the three reports (table 2), it was found that Diatrin had its greatest effectiveness in urticaria, in which 10 cases out of 11 showed improvement. In hay fever, 55 out of 72 cases reported relief, a percentage of 76.4. One case of food allergy reported complete relief. Fair results were achieved in allergic rhinitis. The results in the miscellaneous types (contact dermatitis, allergic dermatitis, vernal conjunctivitis and intermittent hydrarthrosis) were as poor with Diatrin as with the other drugs. However, one case out of the 12 did register improvement. Of the entire 113 cases, only 13 suffered from by-effects with Diatrin. Six of the 13 showed digestive disturbances which may have been induced by the bitter taste of the uncoated tablet.

TABLE II

Hay Fever

Diatrin	No. of Cases	No. of Cases Improved	% of Cases Improved
Preliminary report	12	8	66.7
Supplementary report	30	25	83
Comparative study	30	22	73.3
Combined figures of above studies	72	55	76.4

Urticaria

Diatrin	No. of Cases	No. of Cases Improved	% of Cases Improved
Preliminary report	2	2	100
Supplementary report	—	—	—
Comparative study	9	8	88.9
Combined figures of above studies	11	10	90.9

Allergic Rhinitis (Vasomotor Rhinitis)

Diatrin	No. of Cases	No. of Cases Improved	% of Cases Improved
Preliminary report	7	4	57.1
Supplementary report	—	—	—
Comparative study	10	3	30
Combined figures of above studies	17	7	41.2

Miscellaneous
(Contact Dermatitis, Allergic Dermatitis, Vernal Conjunctivitis)

Diatrin	No. of Cases	No. of Cases Improved	% of Cases Improved
Preliminary report	5	0	0
Supplementary report	—	—	—
Comparative study	7	1	14.3
Combined figures of above studies	12	1	8.3

Food Allergy

Diatrin	No. of Cases	No. of Cases Improved	% of Cases Improved
Preliminary report	1	1	100
Supplementary report	—	—	—
Comparative study	—	—	—
Combined figures of above studies	1	1	100

Total Number of Patients Treated:
Diatrin..... 113
Total Number of Cases with Side Effects:
Diatrin..... 13 (11.5%)

Side Effects of Diatrin on 113 Patients

Type	No.	Type	No.
Drowsiness	5	Abdominal cramps	1
Nausea	4	Palpitation	1
Vomiting	1	Groggy	1
Urinary frequency	1	Tight feeling in chest	1
"Indigestion"	1	Restlessness	1
Running nose	1		

Conclusion

It would appear, therefore, that Diatrin has considerable value as an antihistaminic. The reasonably high symptomatic relief achieved and the markedly low incidence or mildness of side effects make Diatrin an extremely useful antagonist to histamine in many allergic conditions.

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ON THE POSSIBLE APPLICATION OF ISOTOPES TO THE MANAGEMENT OF CANCER*

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THE application of isotopes to the cancer problem can be directed either toward the broad field of investigations concerning the etiologies of neoplastic disease, or toward therapeutic application without fundamental relationship to the causes underlying uncontrolled cellular growth. In this sense it is comparable to the more conventional roentgen-ray or radium therapy now used. It is assumed that any etiologic factors which contributed to the growth prior to therapy are no longer active if the disease can be arrested. It is most unusual for a new growth, unrelated to the first, to develop in the same organ (with the outstanding exception of carcinoma of the skin).

We are well aware that recently the public has been educated to believe that recent advances in atomic physics and chemistry hold much for solving the problem of cancer. This hope finds utterance in both professional and lay journals and forms a part of national and international discussions and plans for the control and uses of atomic energy. As one who has chosen to devote his efforts to the application of radiation to the management of cancer, I am ever more confounded by the number of patients of all cultural levels who look to the newer isotopes for help which cannot be given them by either surgery or the more conventional forms of radiation therapy.

The use of radioactive isotopes has thus far been very limited, despite propaganda to the contrary. In the leukemias and in a few rare cancers of the thyroid gland a beginning has been made in applying the isotopes to the treatment of neoplastic disease. It must be recognized, however, that with these two phases of application our progress to date has been completely described. Without in any way wishing to deprecate the work done thus far, I believe that all of us will recognize that, insofar as the larger problem of cancer is concerned, we have only worked on the fringe of more or less rare forms. The main categories responsible for the high mortality (cancer of the gastrointestinal tract, breast, uterus, lung, etc.) have not been touched. The incurability of leukemia has not been altered, nor is cancer of the thyroid (in itself a rare disease) any the less a serious problem.

What are the chances that the isotopes will have any appreciable effect upon the present cancer mortality when used as radiant therapy? What are the obstacles which make the application so formidable and the picture so pessimistic, as I believe it is?

As we approach the fiftieth anniversary of the discovery of radium and radioactivity, we find ourselves attempting to circumvent those factors which

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long ago caused earlier workers to abandon the introduction of radioactive substances into the system as a means of affecting the growth of tumors. The excellence and detail of the early work on the administration, selective absorption, elimination and pathogenicity of the soluble and insoluble salts of radium, of gaseous administration of radon, the injection or ingestion of salts of mesothorium, radiothorium, thorium, actinium and polonium—these all testify to a serious effort to gain fundamental information in radiobiology and, if possible, to apply it to the treatment of disease. The difficulty lay, however, in the fact that these heavy metals were found largely in the bones, kidney, spleen, liver or lung. There was some, though insignificant, variation in their deposition in tissues when compared one with the other and when envisaged as possible therapeutic agents. The toxic effects, noted particularly in relation to the hematopoietic system, kidney and liver, were such that their use as therapeutic agents was precluded. Such carefully done work did not, however, deter some less prudent individuals from using the newly acquired radioactive substances as therapeutic agents on human victims. The results, though less carefully tabulated, were essentially as disastrous as those previously encountered in experimental animals. Here one would add a note of caution in presently applying available isotopes or compounds containing them to human subjects. One wonders whether we know enough about placental transfer and fetal deposition to give radioiodine to pregnant mothers, as has been done.

Of particular interest to us, since they form the basis for present-day radiobiology applied to therapy, were the early studies upon the biologic action of alpha and beta radiations, and their comparison with those effects already noted for gamma radiation or high voltage roentgen-rays.

As early as 1901, it was demonstrated that the beta rays of radium could be deflected by a magnetic field and that, when caused to impinge upon a bacterial culture, they exerted a bacteriostatic effect which was not obtained by using gamma radiation alone. Likewise, alpha rays from polonium were found to have the same bacteriostatic effect. In 1907, Dominici demonstrated the effect of filtration of the rays emitted by radium when applied to the human skin. He demonstrated that the superficial burn was due to beta and soft gamma radiations, which he called "infra-penetrating rays." By interposing a filter of at least one-half millimeter of lead, he demonstrated that the radiations from radium, thus purified, could be made to have a deeper and more selective effect without producing the more superficial necrotic action. These he called the "ultra penetrating rays.' It thus became possible to apply radiations to tissue with the hope of obtaining reactions more specifically directed toward the offending cells; and from this work there evolved the concept of selectivity of radiation effect, which is the basis for our whole concept of the application of radiation in therapy.

Before entering upon even a brief discussion of the problem of radiosensitivity in relation to the problem of isotopes and cancer, let us again re-

turn to some of the earlier work using the natural radioactive elements. The study by Lacassagne and his associates (1925), on the biologic effects of polonium introduced into the rabbit, is as complete and beautifully conceived a research as is to be found in this present atomic age. Therein was introduced the technic of radioautographs to delineate the tissue deposition of a radioactive element. In addition to a specific study of the absorption, deposition and elimination of polonium, these workers were able to differentiate varying degrees of susceptibility to injury by alpha radiation, whether originating from polonium deposited within the cell or as radiation received from polonium deposited in neighboring cells. Furthermore, they demonstrated that the greatest degree of tissue vulnerability was shown by those tissues known to be most sensitive to roentgen and gamma radiation.

Further studies bearing upon the action of beta radiation introduced into the organism, particularly those by Lacassagne (1921), demonstrated several factors of interest to us in this discussion. By introducing glass capillary tubes containing radon into tissues of varying degrees of radiosensitivity, he demonstrated that the range of effect of beta radiation in space has definite limits and is dependent upon the energy of the radiation. It was likewise shown that the action was a caustic one, to a degree depending upon the dose employed, and that there was little differential effect noted upon different tissues within the same zone of irradiation. The almost instantaneous action of beta radiation was demonstrated by an experiment which placed a glass tube of 70 mc. of radon on the ear of a rabbit for only five minutes. This left a local burn of the same general outline as the tube, but somewhat wider in cross-section, which some two or three months later sloughed, leaving a hole neatly outlining the general form of the tube.

Further studies of beta radiation were made, using the two energies of beta particles emitted by uranium X. It is of interest that this work, published by Lacassagne and his collaborators in 1928, was the only biologic study made of the radiations from uranium which we could find in the literature at a time when uranium hazards were important to the security of our country. They were able to measure the coefficient of absorption of the two groups of beta rays emitted, finding a factor of 7 for the energy of the two beta groups. By placing the mixture of UX_1 and UX_2 in a glass tube, and implanting that tube into the testicle of a dog, they were able to demonstrate a variation in biologic effect dependent upon the energy of the beta radiation. Immediately about the tube they noted a zone of necrosis, which they attributed to the softer radiations, and which was comparable to those effects produced by the beta radiation from radon. An outer zone, exhibiting an "elective cellular effect" upon the more sensitive testicular elements, but without necrosis, was attributed to the higher energy radiations. The tissue reaction in this zone was altogether similar to that seen when the testicle was exposed to gamma radiation. This is not unexpected, since the biologically effective radiations of roentgen and gamma rays are the secondary electrons produced in tissue.

Radiobiologic studies, completed in the first two decades after the discovery of radioactivity, formulated a concept of biologic radiosensitivity which, as far as I am aware, has not been essentially altered. This concept has formed the basis for therapeutic radiation and, until newer evidence is at hand, must continue to be a working hypothesis, whether we use roentgen or gamma rays, the high energy electrons, or the internal emittors of the isotopes. This concept can be briefly formulated as follows:

1. The degree of radiosensitivity of a tissue to ionizing radiation is dependent upon the action of the radiation upon the type of *cells* of which the tissue is composed. Thus in one tissue (i.e., testicle), there may be varying degrees of radiosensitivity to the same dose of radiation, since a tissue may be composed of cells having different origins and functions.

2. The radiosensitivity of a cellular type is not an immutable property—it may change with factors affecting its life cycle, function, or its environmental conditions. Rate of growth, oxygenation, and other factors of metabolism may alter the cellular response to radiation. The wide variation in the susceptibility of the acinar cells of the thyroid gland to radiation in the normal and hyperactive state is an example of this. It is well known, too, that a tissue which is otherwise highly radiosensitive (i.e., lymphocytes) is rendered radioresistant in the process of anoxemia.

3. Apart from the problem of radiosensitivity of cellular elements of a tissue is the interaction of the radiation on the noncellular but living connective tisssue constituents (ligaments, tendons, elastic and fibrous tissue, etc.). These also have a particular radiosensitivity, but of a character different from that of the cellular elements, particularly those with considerable regenerative capacity. The practical importance of the effect of radiation upon these connective tissue elements is the seeming permanence of the process engendered, whether it be one of extreme fibrosis, calcification or decalcification. These changes, being more permanent and by their presence indirectly affecting the cellular substance which they support, are many times the barrier to further radiation or are in themselves the cause for many failures of radiation. A metastatic lymph node, encased and semi-isolated by a dense fibrous wall, wherein the metastatic cells undergo a period of devitalized but eventually renewed growth, is no longer amenable to further effective radiation therapy. Or a local ischemia, due to dense fibrosis of vasculo-connective tissue, may be the cause of necrosis, hemorrhage, infection and death—the cancer having been destroyed.

Guided by this concept of radiosensitivity and the factors which determine it, there has been developed the science of applying ionizing radiation to certain varieties of cancer which *by experience* have been found to be amenable to treatment. The degree of success in each particular variety is dependent upon many anatomic and physiologic factors, but it is fundamentally dependent upon the degree of radiosensitivity of the cells which compose the tumor. As with the whole gamut of the normal cells which make up the

body, so with the malignant ones—there is a wide range and gradation of radiosensitivity encountered among various types of neoplasms. Even in one variety (i.e., teratoma) may be found cellular elements at the extreme limits of radiosensitivity. Or in a cancer composed of one predominantly cellular type (i.e., epidermoid carcinoma of lip, skin, tongue, etc.), there is a wide variation in the radiosensitivity due to environmental or metabolic factors. Epidermoid carcinoma which has invaded bone, or is densely confined in a lymph node, does not exhibit the same response to radiation as does the primary lesion. The former is incurable by radiation, while the primary growth on the lip or tongue is many times controlled. Thus in the practical matter of applying ionizing radiation to malignant disease, if the object is to destroy the cancer without incapacitating injury to the patient, one can hope to succeed only if the cancer is one which has a radiosensitivity which is either greater than or closely parallels that of the normal tissues about it. It is rare that one is able to control a cancer of a lesser radiosensitivity than the tissues in which it is developing.

In returning to the problem of applying the newer isotopes to radiation therapy, it is most appropriate to recollect a statement made by Regaud in 1921. In discussing the attempts previously made to utilize radioactive materials as internal emitters, and in particular the work by Gauss and Lembcke (1912), who made colloidal suspensions of the radioactive heavy metals, Regaud voiced the following hope: "The ideal would be, in the therapy directed against cancer in particular, to introduce heavy metals in the organism which are susceptible of elective fixation in the protoplasm of those cells which one is seeking to destroy and that they would play the rôle of secondary radiators having a range of the order of the molecule. This result may not be impossible of attainment; but the attempts made up to the present time have not been fruitful." This statement, made in 1921 and commenting upon work done in the first decade after the discovery of radioactivity, has the ring of prophecy. Indeed, Regaud lived to see the application of radiophosphorus and radioiodine, and he no doubt followed the newer radiobiology with a keen analytic interest. What he could not foresee in 1921 was the discovery of artificial radioactivity by Joliot-Curie (1934), made in the laboratory adjoining that in which he had spent most of his investigative life. With this discovery, and with the increased scope later made possible by the cyclotron and chain reacting piles, it became possible to envisage the introduction of radioactive substances other than the naturally occurring radioactive heavy metals. This might eliminate one of the most toxic features of previous experimental attempts to use radioactivity within the organism. Furthermore, the possibility of obtaining selective deposition by utilizing the special metabolic requirements of organs and tissues was demonstrated most strikingly with radioiodine. To obtain selectively deposited isotopes with radiations having a range comparable to the molecule of which the isotope is a part is perhaps as yet farther in the future than the time which has elapsed since Regaud's dream in 1921.

It is of interest that the desired range of effective radiation envisaged was of so small an order of magnitude—of molecular dimensions. I would believe that this was chosen for well founded reasons, if one analyzes the interaction of radiation upon living matter, particularly upon the growth of tumors. The best evidence to date supports the theory that the principal effect is *intracellular*, and that, whatever the physico-chemical alterations produced by ionizing radiations, they chiefly result from derangement of intracellular function. To be sure, there are extracellular derangements as well, as we have mentioned in relation to the radiosensitivity of noncellular tissue components. One can also note chemical alterations in the humoral constituents of the organism produced by radiation, but these are, by and large, secondary to alterations in cellular metabolism. If, then, one desires to produce an intracellular action without undue derangement of extracellular tissue, the ideal would select a range of effective radiation at least not greater than cellular dimensions.

Actually we do not know for a fact wherein the cell is most vulnerable and what those intracellular injuries are which lead to cellular death. Of particular interest in this connection is the work of Lacassagne and Holweck (1928) on the quantum absorption of radiation *within* the cell. To quote from one of them:

"These authors demonstrated that in studying those objects wherein cytologic modifications produced by irradiation can be followed microscopically, or even photographically, as in the yeasts and certain protozoa, there was a concordance between the proportion of lesions noted in the cells and that to be expected by the calculation of probability. It was shown that cells as identical as possible, irradiated under identical technics with monochromatic radiation, presented lesions however which were of varying degrees of gravity: in the same field one could find cells which were dead, bordering others which continued to multiply normally with all intermediate degrees of cellular injury being represented.

"The principal steps leading to these alterations were identified and verified in all types studied. These were, in the order of decreasing gravity: immediate death, the suppression of mobility, the suppression of reproduction, abortive anomalies of cellular division, retardation of growth and hereditary malformations.

"Under strict experimental conditions it thus became possible to calculate—for a specific cellular type whose morphologic character was known (in particular the volumes of motor centers, centrosome, nucleus, cytoplasm, etc.)—the probable distribution of photoelectrons which, for a given irradiation, would respectively affect each cellular component. . . . Each of the principal types of radiolesions was found to be proportional to the volume which each special region occupied within the cell.

"Envisaged from this aspect, cellular radiosensitivity appeared as being, for each type of cell, a function of two principal factors: (1) the histologic

texture which conditions the respective volume of the sensitive zones which the ionizing projectiles affect to produce the specific lesion; (2) the physicochemical composition which conditions the number of projectiles necessary to produce the molecular disintegration of intracellular components."

I have taken considerable time to elaborate these observations because they have an important bearing upon the application of isotopes in radiobiology. They are of interest particularly because they attempt to explain the many *inequalities* of radiation effect. They shed some light upon the great discrepancies noted in attempting to ascertain a "lethal dose" for a particular cell type. It is often difficult completely to destroy a tissue, even though it is apparently very radiosensitive. Because of the inequalities of cellular injury, it may necessitate a dose far in excess of that required to produce the death of the great majority of cells of which the offending tissue is composed. Thus far, with external radiation or implanted radium, it necessitates some degree of injury to neighboring normal tissues if total eradication of the undesired cells is to be obtained.

In this respect I believe we can say that, with present day equipment available for radiation therapy (medium and supervoltage roentgen therapy, radium), we are not confronted with the problem of being unable to deliver a cancericidal dose to tumors whose radiosensitivity is such that they are within the realm of control. With supervoltage roentgen-rays the skin has no longer remained a limiting factor in applying roentgen radiation to deep-seated tumors. Rather, however, we are many times stopped from introducing a truly lethal dose because of the possibility of damage to vital tissues immediately about the tumor. In irradiating from the exterior into the tumor this barrier is most pronounced. Interstitial implantation can in a limited number of instances overcome the difficulty. Internal emitters could *theoretically* overcome this obstacle in radiation therapy under certain conditions.

The depositon of the isotope should then be selective for the tumor and lodge *within* those cells which form the cancer. Its range should be one which does not over-irradiate neighboring tissues and, as before noted, the ideal range would be one of cellular dimensions. This not being possible, at least the range must in many instances be such that neighboring tissues are not necrosed. For some tissues which border on a growth (i.e., muscle), this may not be important. For others (i.e., bowel, large blood vessels) it may, as with external roentgen therapy, be the cause for failure if the tumor dose is sufficiently elevated. Since the range of the radiator will be independent of the volume of the tumor, intricate problems in dosimetry are posed for neoplasm and neighboring tissues.

The problem is best illustrated by example. Let us suppose that radioisotopic investigators had made available to us a radioactive compound with specific affinity for the epithelial cells of squamous carcinoma. Not to make the supposition seem too remote, let us assume that the radiator was emit-

ting Beta particles of a range comparable to that of P^{32}—approximately 7 mm. in tissue. The half-life we will omit, since it is not particularly pertinent to this phase of the problem. Let us see what obstacles we might meet if we planned to use this radioactive substance in treating one of the most common squamous carcinomas, namely, a cancer which has arisen in the cervix uteri, invaded the broad ligaments of the pelvis and infiltrated along the course of one ureter, and has deposited in lymph nodes resting over the bifurcation of the aorta. If there is an optimum "lethal dose" for squamous carcinoma so described, let us assume for purposes of discussion that it will be in the range of 6000 r if delivered in a time which is not less than two to four weeks. By its anatomic invasion tumor cells may be less than 5 mm. from several vital structures (ureter, iliac vessels, aorta, urinary bladder, intestines, rectum). If the tumor is to be controlled, then *all* malignant cells must be sterilized, and this includes those on the periphery adjacent to vital structures. The problem returns to that which confronts us with external irradiation: how to avoid injury to normal and vital structures, yet adequately irradiate the tumor. If the wall of the small intestine, or the ureter, received from the cancer cells which lay in contact with it a dose of 6000 r, the cancer cells might be devitalized but so, most likely, would the bowel and the ureter. These are the dilemmas which cause us to fail in about 95 per cent of cancer of the cervix at the stage of advancement which I have described. These, and ones only slightly less advanced and posing the identical problem as to radiation therapy, account for over half of the cancer of the cervix coming for treatment.

The obstacle here lies largely in the range of effective radiating energy of the radioactive substance. Let us look at tritium, the newly discovered isotope H^3. It is a radioactive isotope whose effective energy permeates tissues in dimensions of microns, ideal as an intracellular radiator. Its half-life is long, and, being hydrogen, it can expect to be incorporated into the molecular structure of most tissues. The ingenuity of biochemistry is indeed severely taxed to affect specific localization of tritium into malignant cells only and to cause its elimination from the body with safety once its cancericidal mission is accomplished.

Another formidable obstacle is related to the previous discussion. Can it be expected that the use of the radioisotopes will enlarge the scope of radiation therapy by applicability to a wider range of tumors? This relates to the problem of radiosensitivity previously mentioned. Radiation therapy is at present limited to a minority of cancers because, by experience, these have been found to be the only ones with a radiosensitivity favorable to this approach. The glandular cancers (gastrointestinal tract, breast, kidney, prostate) are by and large incurable by any form of radiation now used, regardless of the age or size of the growth. These also are the cancers which account for over one-half of the present mortality from cancer. Will the advent of a substance which selectively deposits within cancer derived from

the mucous membrane of the stomach alter in any way the radiosensitivity of these cells? It is not to be expected that it will, if we impute to the electrons secondary to roentgen and gamma rays the rôle of ionization and biologic effect common to all ionizing radiations. This is a problem apart from dosimetry; it is one of cellular peculiarity which cannot thus far be altered in a more favorable direction. We know ways to reduce a favorable radiosensitivity and must be cautious to avoid these errors in therapy. We know of no practical means to increase the inherent vulnerability of cells to radiation.

I have not touched on a further obstacle which seems even greater than any of those so far posed. This relates to selective deposition. Radio-iodine is unique thus far in this respect, but here in most instances of cancer of the thyroid the deposition in the cancer is less than that in the healthy gland, as was first demonstrated by Hamilton. There are rare instances of deposition in certain functioning forms of thyroid cancer, but this is less predictable. Radiophosphorus has not in any way altered the mortality from the lymphomas because it is not selectively deposited within those cells which are the malignant ones. It is deposited generally throughout diseased and healthy cells of a group of tissues, and the limitation of its effectiveness is largely due to its non-selectivity among cells of the same tissue.

My imagination does not permit me to envisage means for selective deposition of a radioactive substance which will have a tropism for only the malignant cells of an organ or its metastatic foci—unless research is able to identify a substance common to cancer, or a particular variety of cancer, which can be tagged with a radioactive therapeutic isotope.

There are still other obstacles to be overcome. The carcinogenic properties of certain isotopes and newly discovered elements are well known to those familiar with the subject. There is already suggestive evidence that there may be a higher rate of eventual leukemia among the group of polycythemias treated by P^{32}.

The purpose of my remarks is not to discourage investigation which may lead to useful application of the isotopes in cancer therapy. I have not touched upon their important rôle in research on the etiology of cancer. I have only tried to be realistic in stating certain obstacles to the problem of using isotopes in therapy, so that we and the public may not expect too much within our children's lifetime. If we realize the magnitude of the problem, then there can be a wiser choice of investigations which attempt to apply the isotopes to the whole problem of cancer, concerning both its causes and treatment.

CASE REPORTS

A FATAL CASE OF APLASTIC ANEMIA FOLLOWING CHLORAMPHENICOL (CHLOROMYCETIN) THERAPY *

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Chloramphenicol (chloromycetin) has been widely used as an effective antibiotic with little regard to the possibility that it might cause serious toxic reactions. As is sometimes true with new preparations, these reactions may not appear until the drug has been administered to a rather large group of patients. We wish to report a case of fatal aplastic anemia following the prolonged administration of chloromycetin. As far as we can determine, this is the first report of such a reaction occurring during the use of this antibiotic.

Case Report

A white male, age 63, was admitted to St. Elizabeth's Hospital on December 14, 1949, because of a purpuric rash which he had first noted the preceding day. His illness began on August 2, 1949, with fever, chills, some urinary burning and frequency, and general malaise. He was given oral penicillin and the symptoms promptly subsided. On August 9, his prostate was found to be somewhat enlarged and his urine contained many pus cells. The next day, because of the pyuria, he was started on Citrasulfas (Upjohn), 2 gm. daily. On August 14 this was increased to 3 gm. daily. The pyuria persisted, and on August 19 this medication was stopped and he was hospitalized for intravenous pyelography. An incomplete filling of one of the minor calices of the upper pole of the right kidney was noted, but the findings otherwise were not remarkable. He was given penicillin, 400,000 units daily from August 29 to September 7. From September 10 to September 14 he again was given Citrasulfas, from 1 to 1.5 gm. daily. On September 19 his urine again contained many pus cells, and he was started on chloromycetin. For 48 hours he was given 0.5 gm. every six hours, following which he felt much better and it was noted that his pyuria was greatly improved. The dose then was decreased to 0.25 gm. every six hours for two days and then to 0.25 gm. every eight hours. This dosage was continued until October 2. Two days later, pus cells again appeared in his urine. He was again placed on chloromycetin, and he took from two to three capsules daily until October 24, when the local supply of this preparation was temporarily exhausted. For two days he was given aureomycin, 0.25 gm. three times a day; then, as chloromycetin again became available, it was resumed at a dose of three capsules a day until November 8, and then two capsules daily until November 29. For the next three days he was given mandelamine, but since the pyuria returned as soon as the chloromycetin was stopped, the latter was resumed on that date and continued at one capsule three times a day until December 13, at which time the purpuric rash was first noted. During all this time

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he had no other medication, except an occasional tablet of creamalin. He was very emphatic that he had taken no sedatives, analgesics, or antihistaminics.

Physical examination on admission to the hospital showed a generalized purpuric rash which was most marked on the lower extremities. Several ecchymotic areas were present on his legs and hands, and petechiae were noted in his conjunctivae. The liver and spleen were not enlarged. Blood pressure was 154 mm. Hg systolic and 108 mm. diastolic. The remainder of his physical examination was not remarkable.

The erythrocyte count on admission to the hospital was 4,100,000, with 11.5 gm. hemoglobin. The leukocyte count was 5,250, with 21 per cent neutrophils and 79 per cent lymphocytes. The platelets were markedly diminished. Urinalysis showed no albumin or sugar, and microscopic examination showed 1 to 2 pus cells per high power field, 5 to 6 red cells, and an occasional hyalin cast. Examination of a smear of his sternal marrow showed that it was very acellular. Practically no myeloid elements were seen, and there were no megakaryocytes. A count of 100 nucleated cells gave the following: adult neutrophils, 2 per cent; eosinophilic myelocytes, 3 per cent; adult lymphocytes, 63 per cent; megaloblasts, 1 per cent; intermediate normoblasts, 14 per cent, and late normoblasts, 17 per cent.

TABLE I

Date, 1949	RBC	Hb. in Gm.	WBC	Platelets	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils
Aug. 25	3,820,000	12	12,650	—	73	25			2
Sept. 12	4,120,000	12.3	15,000	—	78	19	1	1	1
Dec. 13	3,750,000	12.4	5,100	markedly diminished	18	75	1	5	1
Dec. 14	4,100,000	11.5	5,250		21	79			
Dec. 15				markedly diminished	6	90	4		
Dec. 17	4,120,000	12	4,100	80,000	2	95		3	
Dec. 19	2,620,000	8.5	3,150	40,000	8	92			
Dec. 21	2,640,000	8.0	2,200	80,000	20	80			
Dec. 23	1,860,000	5.5	2,550	11,000	8	92			

During the first four days of his hospitalization, the patient did not seem severely ill. On December 18, he passed a large tarry stool, and he developed a fever of 101.8° F. From this time on his course was rapidly downward. His red count fell in spite of daily transfusions of 500 c.c. of whole blood. He developed a severe herpetic lesion on his upper lip, new showers of petechiae appeared daily, and he continued to have gross melena. His temperature reached 103° each evening, he became progressively weaker, and he finally died on December 24. His treatment consisted of aqueous procaine penicillin, 400,000 units daily for the first five days and then 800,000 units daily; folic acid, 10 mg. daily; vitamin B 12, 30 micrograms daily, and Armour's yellow bone marrow concentrate, 4 c.c. six times a day. A résumé of the blood counts taken during his illness is shown in table 1.

NECROPSY

Throughout the skin of the trunk and extremities there were many petechiae. Bruises surrounded venipuncture wounds, and the left index finger was purplish-blue and swollen at its base. Confluent petechiae extensively flecked the diaphragmatic pleurae, the gastric mucosa, and the epicardium; ecchymoses were seen in the serosa of the gall bladder and in the urinary bladder mucosa. Moderate numbers of petechiae were located in the cardiac septa and kidney framework, and in the colon there was a hemorrhagic polyp.

Although liberal quantities of reddish-tan marrow could be expressed from the sternum and vertebrae, microscopically, there was a marked reduction of hematopoietic elements. Cellular islands were small and widely separated by normal marrow fat. Readily recognizable deviations from normal in these islands, which consisted chiefly of closely packed, large and small basophilic cells, were the absence of megakaryocytes and the paucity of granulocytic cells. Considerable difficulty was encountered in labeling individual cells, as seen in Giemsa stained sections of undecalcified marrow, for within clumps all gradations could be observed between cells of different categories. An approximate differential count revealed the following cellular array: cells having dark small nuclei with scanty basophilic cytoplasm, regarded as normoblasts, 9 per cent; somewhat larger cells with a coarse chromatin network and moderate amounts of basophilic cytoplasm, as lymphocytes, 37 per cent; large cells with basophilic cytoplasm, eccentrically placed nuclei with peripheral condensation of chromatin and only occasionally a perinuclear halo, as plasma cell-like, 30 per cent; still larger basophilic cells with large vesicular nuclei having scanty fine chromatin and large nucleoli—sometimes in mitosis, as stem cells, 15 per cent; myelocytes, basophilic and chiefly eosinophilic, 3 per cent; and finally, those regarded as reticulum cells, some of which were phagocytic and contained hemosiderin, 5 per cent. Cells considered as plasma cell-like had some features of the nuclear pattern of erythroblasts. Yet the large size, eccentricity of the nucleus, rare ones with a perinuclear halo, and the pronounced basophilism of the cytoplasm were more suggestive of the adult plasma cell than an erythroblast. Degenerating plasma cells were not observed.

The spleen weighed 140 gm., and its substance was light red, firm and with normal markings. The splenic follicles were small and apparently reduced in number. Often the central arterioles presented acidophilic hyalin substance beneath the endothelium, and in some follicles strands of similar substance were intertwined between lymphocytes. The pulp was reduced in content and the sinusoids were dilated and lined by prominent littoral cells. There were increased numbers of monocytes and plasma cells throughout the pulp. Macrophages, some containing phagocytosed erythrocytes and others laden with hemosiderin, were found in the sinusoids. Rarely, large binucleate, basophilic, somewhat hyalin cells were seen in the sinusoids. There was serosal cuboidal metaplasia of the capsule.

The para-aortic and mesenteric lymph nodes were slightly enlarged, hyperemic and moist. Microscopically, these and a bronchial lymph node had much the same changes as seen in the spleen. There was considerable spillage of erythrocytes into the sinusoids and, focally, there were infiltrations of lymphocytes and monocytes into the capsules. Throughout the adventitial tissues there was moderate edema which also involved vascular walls.

The lungs weighed 585 and 965 gm., right and left, respectively. The larger bronchi were filled by ropy, reddish-tan, friable, loosely adherent substance. The bronchial linings were hemorrhagic and the lumens slightly dilated. The lung substance was dark-red, boggy, and oozed bloody fluid. Throughout all bronchial divisions there was a profound change of approximate equal intensity and age. The initial lesion, as seen in rare bronchioles and in persisting glands of the larger bronchi, appeared to be one of interepithelial and subepithelial edema. This was followed by mucosal sloughing and the development of foci of edema and fibrin precipitation in the wall. Generally, the bronchi presented lumens filled by coagulated protein, some fibrin threads and erythrocytes. These luminal masses were surrounded by necrotic mucosal cells. About many of the bronchi and the bronchioles, particularly in relation to the lung roots, there were clusters of hemorrhagic alveoli with focally necrotic walls. In those bronchial divisions with more marked involvement there was thrombonecrosis of small veins.

The heart weighed 335 gm. There was slight fibrosis of the aortic and mitral valves and associated chordae tendineae. Minute fibrous tags arose from the aortic nodes of Arantii. The serosal and endocardial cells were moderately swollen, and some of the myocardial arterioles were edematous. Stigmata of past rheumatic disease and cloudy swelling were seen in the myocardium. Within the cardiac septum, often subendocardially and rarely in the interstices of the neuromuscular tissue, there were extravasations of erythrocytes. In the anterior left papillary muscle there were more profound changes. Here there were variations in the staining and fragmentation of muscle fibers, broad, intensely acidophilic intercalated discs, and focally, granular, and globular disintegration of fibers. These intense changes were not found to be related to either hemorrhage or marked vascular edema, but in several foci the necrotic fibers were being invaded by masses of bacteria, not accompanied by inflammatory reaction. Foci of inflammation, however, were seen beneath the endocardium. These were sparse, loose collections of monocytes, plasma cells, and myocytes. Aschoff cells were not seen.

The liver weighed 1,510 gm. and consisted of yellowish-brown firm substance. The vascular markings were accentuated. Foci of necrosis were scattered throughout in relation to central and sublobular veins. The contiguous liver cells were fairly well preserved and the cords intact with closely applied sinusoidal endothelium. Small numbers of hepatic cells presented nuclear glycogenic infiltrations. The foci of necrosis were characterized by a marked loss of hepatic cells, a condensation of stroma, scant persisting degenerating liver cells, and moderate numbers of lipochrome-laden macrophages. There was a slight increase in the number of plasma cells in the portal triads, and an occasional portal vein contained clumps of bacteria.

The stomach was distended by gas and a large amount of brownish-red fluid. There was ileus; the small intestine contained grayish-black semifluid substance and the colon, tarry stool. A hemorrhagic polyp was present in the colon and a 3 cm. carcinomatous ulcer was found in the prepyloric portion of the stomach. The base of this neoplastic ulcer was formed by a thick necrotic zone heavily laden with masses of bacteria. Inflammatory reaction was absent. Similar mucosal necrosis was seen focally in the colon. In some regions, the necrotizing reaction extended laterally beneath the mucosa and implicated submucosal vessels, some of which contained masses of bacteria. The mucosal surface of the hemorrhagic sigmoidal polyp was necrotic and invaded by organisms. Gram stain revealed a mixed bacterial population. Elsewhere in the gut there were sloughing of mucosal cells, edema of glandular epithelium and a decreased cellularity of the lamina propria, with a relative increase of plasma cells and eosinophils.

The adrenals were grossly normal. Microscopically, there was a depletion of lipid droplets. Within the medulla there were small collections of lymphocytes and petechiae. Irregular spaces up to 100 microns, sometimes containing sparse acidophilic granules and degenerating epithelial cells, were seen in the outer thirds of the cortical columns.

The kidneys weighed 425 gm. The cortices were swollen, yellowish-tan and indistinctly delimited from the pyramids. Large subepithelial pools of extravasated blood were present in the peripelvic tissues. Some of the distal convoluted tubules presented hemoglobin casts along with segmental dilatation. Generally, the renal architecture was well preserved, except for small cortical and corticomedullary scars rather heavily infiltrated by macrophages and some plasma cells. A similar infiltration of lesser extent was present in the peripelvic tissues. There was moderate dilatation of the convoluted tubules, with only slight granularity of the tubular epithelium. Bowman's capsules were characterized by marked epithelial edema. The bladder mucosa and lamina propria presented changes like those in the renal pelves.

The prostate was moderately enlarged; the left lobe was about twice the size of

the right. The left lobe was soft and mottled reddish-tan, whereas the remaining substance was firm, nodular, and yellow-white. Minute calculi were seen in the prostatic ducts. Within the left lobe, the acinar epithelium was sloughed and necrotic; in some foci, swollen anuclear distended granular cells lined acini filled with eosinophilic granular and globular debris. Large and small collections of macrophages with some plasma cells were moderately distributed in the stroma and in relation to necrotic epithelial masses. Generally, the small vessels were occluded by recently formed thrombi. The framework was edematous and hemorrhagic, and clumps of viable smooth muscle cells were sparse.

Microscopically, the posterior portion of the prostate showed a marked periacinar infiltrate of lymphocytes and macrophages. Two granulomas were also found, one to two low power microscopic fields in diameter. These were poorly delimited and were formed by closely packed, unoriented epithelioid cells, lymphocytes, fibroblasts, and many foreign body giant cells. One was centrally caseous. Acid fast and Gram stains were negative for organisms.

The brain weighed 1,350 gm. There were evidences of moderate edema, and sections presented increased lipochrome content of the ganglion cells of the medulla and basal nuclei. Moderate numbers of amyloid bodies were found in the peripheral portions of the medulla and periventricularly. Slight satellitosis and neuronophagia were noted in the cortex.

The final diagnoses were: aplasia of the bone marrow; moderate hyperplastic lymphadenitis; slight hemosiderosis of the spleen and bone marrow; visceral evidences of shock, anoxia, and sepsis; infarction of the prostate; mild chronic pyelonephritis; chronic and focal granulomatous prostatitis.

Other diagnoses of note were: adenocarcinoma of the stomach; foci of pulmonary anthracosilicosis; healed rheumatic endocarditis; generalized arteriosclerosis and arteriolosclerosis.

Discussion

Although there are numerous reports of various therapeutic agents capable of depressing or destroying bone marrow function, little has been said of their manner of action in this regard. Thus the same basic injury can be produced by radiant energy, benzene and some of its derivatives, inorganic arsenic, and colloidal silver, bismuth and mercury. It has been suggested that those organic compounds which have a benzol ring with an attached amino or nitro group, being readily oxidizable, are capable of producing bone marrow depression.[1] This type of toxic reaction, as produced by benzene or its compounds, shows extreme variation in individual susceptibility, in the interval between last exposure and pathologic change, in the size of the dose, and in the degree and type of response.[2] The factors which prevent normal enzymatic action necessary for orderly maturation of marrow cells being unknown,[3] the reactions to various organic agents have been ascribed to sensitization, even though a long interval may have existed between the last exposure and marrow impairment.[2] The absence of peripheral and marrow cell destruction strongly suggests that there is a failure of formation at primitive levels, yet the sudden depletion of peripheral blood cells implies a direct toxic action.[4] Finally, in severe cases, the effects of bacterial toxins and those from degenerative and necrotic visceral changes, along with the effect of anoxia from lack of erythrocytes and shock, greatly embarrass any regenerative attempts by the remaining hematopoietic units.

Reflecting the unsettled state as to the normal maturation of bone marrow cells, there is considerable confusion in the use of terms for identification of the

persisting cellular elements as seen in hypoplastic or aplastic marrow. In some reports, the terms lymphocyte and primitive cell are used interchangeably; often there is mention of plasma cells in profusion, yet others identify these as abortive erythroblasts [5] or as plasmacytoid cells [6]; large framework cells may be described as reticulum cells or as stem cells, and the latter as megaloblasts or lymphoblasts. Perhaps part of the difficulty resides in the attempt to classify cells in terms of an assumed normal maturation series, for it has been pointed out [5] that:

"It is possible on the basis of these criteria to select a lymphoblast in the spleen or in a lymph node which differs from a myeloblast of the marrow; it is further possible to select among myeloblasts, ancestral cells of granulocytes, monocytes, and erythrocytes which appear to show differential features. But to emphasize such differences, cells must be selected, and variations within each group must be ignored. And the criterion employed by some to judge the specific character of these ancestral cells, namely, by the 'company which they keep' must be recognized for what it actually is; an evasion of the fundamental issue, an interpretation without morphologic or cytologic validity."

Special stains for the presence of oxidizing and proteolytic enzymes have been found wanting as another method of differentiating cells morphologically similar.[7] The suggestion has been made that cells are seen which are unlike normal marrow components and that the exact relationships of these cells to hemopoietic development is not clear.[8] In some late cases of aplastic anemia there may be extreme regenerative hyperplasia, occasionally leukemic, or myelofibrosis with sequestration of abnormal multinucleated giant cells.[2] It appears, then, that although there may be superficial resemblances to normal marrow cells, those present in hematopoietic foci of cases of aplastic anemia are abnormal in structure and function.

The marked increase in lymphocytes and plasma cells may represent cells filtered out of the blood stream or they may be of local origin. The plasma cells might reflect abnormal blood proteins [2] or represent abnormal erythroblasts, as suggested on the basis of comparative embryologic studies.[5] If the lymphocyte is filtered out by the bone marrow, then aplastic anemia represents the inability to convert such cells into erythroid and granulocytic elements. It appears more likely that lymphocytes are of local origin on the basis of embryologic investigations, as, in the lower forms, lymphoid and myeloid tissues are potentially one and the same.[8, 9] Certain cases of chronic agranulocytosis, which eventually develop aplastic anemia, are indicative of the pluripotentiality of the lymphocyte.[8]

Despite a vast literature on aplastic anemia, there is a paucity of complete necropsy reports on such cases. Visceral changes, when striking, are often attributed to direct action of the agent. The changes in this case are similar to many of those observed in atomic bomb casualties dying in the third to sixth week inclusive,[6] of benzene,[2] of atabrine,[10] of sulfonamides,[3] and of arsphenamines.[11] The occurrence of similar lesions in the viscera of cases dying in the first 48 hours after the induction of hyperpyrexia [12] casts considerable doubt on the ascribed specificity of particular chemical agents in the production of certain visceral changes. Some of the factors common to these varied classes of injury are anemia and impaired circulation with resultant stagnant anoxia, infection with accompanying toxemia, and an accumulation of degradation products from widespread tissue necrosis producing a toxemia which, either alone or in combination with the other two factors, is responsible for death.[12] In all of these instances, the longer the survival the more pronounced are the changes.

Penicillin therapy probably contributed largely to controlling infection in this case, for only small bacterial masses of mixed population were found in the tributaries of the portal vein, the splenic sinusoids, the bone marrow and the bronchi. Massive focal infection was present in the stomach and colon. Even though the lymphoid tissues were relatively well preserved, there was no response on the part of lymphocytes or monocytes, except in the heart, to these infected foci. That there should be a failure of combative response is understandable in view of the granulocytic aplasia; failure of the lymphoid system to respond, however, implies a functional impairment of the remaining reticulo-endothelial system without significant morphologic change. Not only is there inability to respond cellularly to noxious agents, but also there is reduction in the ability to form antibodies.[14] This total failure of the defense forces indicates that the complication of infection in these cases cannot be controlled solely by chemotherapy; efforts must also be directed at preventing anoxia and shock so that there will be no loss of mucosal integrity with subsequent bacterial invasion and the development of visceral degenerative and necrotic changes.

The diffuse hemorrhages noted within the skin, mucosa and viscera are not related solely to the marked reduction of platelets, but also are the effects of shock and anoxia. Hyperemia, vascular paralysis, edema and hemorrhages are concomitants of anoxia and shock, which in this case were as significant as thrombocytopenia in the terminal phase.

The disseminated foci of necrosis in the liver as seen in some cases of marrow aplasia, regardless of cause, appear to be late events, since jaundice does not as a rule develop. Similar lesions were noted in fatal cases of hyperpyrexia, and in such cases jaundice developed only in those who lived longer than 48 hours after the induction of fever.[12] Such liver lesions, whether occurring as a postradiation effect, or as the result of hyperpyrexia or atabrine have a striking resemblance to those of virus hepatitis.[6, 12, 10]

The observed microscopic changes in the adrenals are again probably a terminal event and are to be regarded as effects of shock, anoxia and toxemia.

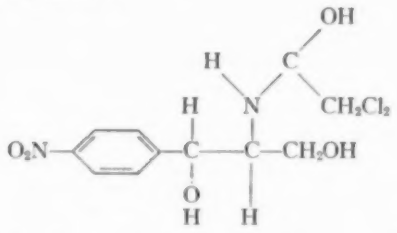
The profound pulmonary changes seen in this case have been referred to as "neutropenic pneumonia."[6] In various reports there has been brief mention of bronchopneumonia, "abscesses devoid of leukocytes" and "pneumonic exudates containing relatively few polymorphonuclears."[3, 11, 10, 2] Bacterial invasion was scanty and, when present, was found in the bronchial casts. Sludging of capillary blood was noted in the small foci of pulmonary hemorrhage and in the more severely involved bronchial walls. The necrosis of the bronchial mucosa and the bronchial casts are not interpreted as phenomena related to inflammation, but are considered as effects of toxemia, anoxia and shock. That bacterial invasion was not more pronounced suggests that this event was late. The obstruction of the bronchial tree by this protein-rich fluid is thought to be the immediate cause of death.

Several factors should be considered in determining the agent responsible for the aplastic anemia which this patient developed. It is true that an early gastric carcinoma was discovered at autopsy which was unsuspected clinically. However, we found no evidence of any metastatic lesions and we do not consider it likely that this early tumor played any part in his final illness.

A review of his medication reveals that he was given a sulfonamide prepara-

tion for a period of 10 days, four months before the onset of his final illness, and one month later he again received small doses for a period of four days. A blood count at this time showed a moderate neutrophilic leukocytosis and no evidence of marrow aplasia. It would be most unusual for a blood dyscrasia to develop three months after the last administration of a sulfonamide, and we do not believe it played any rôle in this case. The only medication which he received in the final three months of his life, with the exception of chloromycetin, was an occasional tablet of creamalin, and several doses of methanamine mandelate (mandelamine) two weeks before the appearance of his purpura. Both of these substances have been used extensively for a long time with no instances of blood dyscrasias reported following their use, and for this reason we do not feel that either could be responsible.

We are left, then, to consider the possible rôle which chloromycetin might have played. This substance was originally prepared from filtrates obtained from *Streptomyces venezuelae*. According to Rebstock, Crooks, Controulis and Bartz,[15] its structural formula is:



Smadel [16] stated that the presence of the nitrobenzene radical in the structure of chloromycetin led to the suspicion that the drug might be toxic for the hematopoietic system. He stated that no serious toxic manifestations have occurred as a result of chloromycetin therapy; he realized, however, that the drug is only now coming into wide usage, and he felt that careful search for such manifestations should be continued. Volini, Schwartz et al.[17] reported three patients in whom there was evidence that chloromycetin produced a marrow hypoplasia more marked in the granulocyte series but also involving a maturation arrest of erythroid elements. Their patients had received chloromycetin for periods ranging from nine to 19 days, and white cell counts as low as 3,000 and absolute neutrophil counts of 264 were observed. In all their patients, there was an immediate spontaneous reversal of the downward trend in blood values upon discontinuance of the chloromycetin.

We feel that the weight of evidence points to chloromycetin as being the responsible agent in our case. In support of this are the facts that he had received no other medication known to have caused blood dyscrasias for three months prior to the onset of his aplastic anemia, that chloromycetin contains a nitrobenzene radical and other compounds containing this radical have frequently caused severe hematopoietic disturbances, and, finally, that previous observers have noted a depressing effect on the marrow in patients taking this substance. It would seem advisable to have repeated blood counts made on patients who receive chloromycetin over prolonged periods.

Summary

A fatal case of aplastic anemia following prolonged chloromycetin therapy is reported, together with complete autopsy findings. The rôle played by different physiologic mechanisms in producing the resulting pathologic picture is discussed. It is felt that chloromycetin was probably responsible for the marrow aplasia in our case, since it contains a nitrobenzene radical and is therefore potentially dangerous to the hematopoietic system. The occurrence of such a reaction makes advisable repeated blood counts on patients who receive chloromycetin for long periods.

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SEVERE POLYNEURITIS FOLLOWING GOLD THERAPY FOR RHEUMATOID ARTHRITIS *

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THE use of gold salts continues to be a mainstay in the treatment of rheumatoid arthritis. This is so despite the well-known dangers of toxicity of these compounds, and the fact that their use is still on a purely empirical basis. In view of their highly probable therapeutic value, the employment of these drugs is justifiable if due regard is given to the danger of their use.

Recent observations would indicate that BAL [1, 2, 3] may prove a safe and effective means of counteracting serious complications. A case of severe polyneuritis occurring in the course of therapy of rheumatoid arthritis with gold sodium thiomalate (Myochrysine) is reported. This type of complication of gold therapy is rare as compared to the relative frequency of those involving other systems or structures in the body.

CASE REPORT

A married white man, aged 28, who had enjoyed good health spent "almost all day digging out a tree" in November, 1945. Two days later his back "started stiffening up" and he found it difficult to get out of bed, to sit down, or to get up. Over the right sacral region he had a dull pain that was aggravated by movement. He was put to bed on a hard mattress, allowed toilet privileges, and "treated with lights." By the end of 48 hours the backache was "almost gone." Subsequently he suffered recurrences of sacral pain on lifting or other muscular strain.

Late in February and early in March of 1946, he went skiing on three occasions and found that he was more subject to aches and pains from strain than before and recovered more slowly. After the last episode of skiing he was "very sore and uncomfortable." When he developed a dull aching pain throughout the back and in the shoulders in April he consulted a physician. "Most of the time" his temperature was one-half to one degree above normal. The sedimentation rate is said to have been "high." Two "suspicious" teeth were extracted.

Early in May considerable swelling of the right knee associated with pain and limitation of motion set in gradually. About a week later he fell downstairs and forcibly bent the knee. The swelling of the knee left directly, only to be followed by "a hard ache" in both ankles without swelling, and by pain in the upper and lower limbs which was confined chiefly to the joints.

On June 12, 1946, he was referred to one of us (E. F. C.). The left knee exhibited mild swelling and tenderness, with pain on movement of the patella. Both ankles were slightly swollen and were painful on active and passive motion. His temperature was 99.2° F. The sedimentation rate was 15 mm. in one hour (Cutler method). Urinalysis and complete blood count gave values within normal limits. A diagnosis of rheumatoid arthritis was made.

The patient was given four intramuscular injections of 100 mg. of Myochrysine at weekly intervals. After the third injection he was relieved from symptoms until just before the next injection was due.

For several days prior to his visit on July 10, he had a mild "rash" on the neck and chest and felt feverish. At the time he came to the office he complained of itch-

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ing but exhibited no rash. His temperature was 99.2°F. Urinalysis was negative. The leukocyte count was 5,500. On July 10, and every seven days thereafter until August 7, he was given additional intramuscular injections of Myochrysine in doses of 100 mg. In all, he received 900 mg. of Myochrysine, or 450 mg. of gold, with what were considered very satisfactory therapeutic results.

On August 10 the patient awakened with tingling and pricking of the hands, wrists, feet and ankles, which gradually grew more pronounced. During the second week he began to grow tired and to show incoördination of the upper and lower limbs. By the end of the second week the paresthesias had progressed proximally to the elbows and knees. He could walk short distances only with much difficulty. At the beginning of the third week he "gave up and went to bed." The paresthesias spread upward to involve the thighs, the upper limbs and "part of the rib cage." He became unable to feed himself. About that time the pain in the back returned. For a week beginning September 5 he had difficulty starting the urinary stream. Immediately afterward improvement became apparent. By the time the patient was admitted to The Hospital of the Good Samaritan, Los Angeles, on September 15, 1946, the girdle sensations had almost disappeared and control of the hands had become slightly better.

On examination by one of us (J. B. D.) at that time, the weight was 156 pounds, the blood pressure 148 mm. Hg systolic and 100 mm. diastolic, and the pulse rate 96. The temperature was normal during the time he was in the hospital, except on the afternoon of September 16, when it rose to 99.6° F. Moderate limitation of movement of the cervical and lumbar portions of the spine, and tenderness on percussion over the spine below the level of the angles of the scapulae were noted. The ophthalmoscopic examination was negative.

There was moderate weakness of the hands and forearms and slight weakness of the arms and shoulders, slight to moderate weakness of the feet and legs, and very slight weakness of the thighs and hips. Sensations of light touch, superficial pain, and warmth and cold were slightly to moderately diminished distal to fading levels at the middle of the arms and around the junctions of the middle and upper thirds of the thighs. Stereognostic sense was lost. Sense of position and passive movement was abolished at and distal to the elbows and was much diminished at the shoulders. It was moderately reduced at the big toes. Vibratory sensation was not perceived over the metacarpal bones or elbows, was moderately diminished over the malleoli, and was essentially normal over the iliac crests.

There was marked incoördination of the upper limbs, with a slight degree of adiadokokinesis, pronounced dysmetria, and writhing movements of the fingers. The gait was moderately ataxic. The biceps, triceps, supinator, patellar and achilles reflexes were not obtained even on reinforcement. No response was obtained on plantar stimulation of the left foot. Only a feeble response in flexion was obtained from the right foot. The patient was somewhat apprehensive.

The cerebrospinal fluid obtained by lumbar puncture showed normal hydrodynamic values and reactions. The Wassermann tests gave negative results. There were three lymphocytes per cu. mm. The concentration of the total protein was 45 mg. per 100 c.c.; of the sugar, 65 mg., and of the chlorides, 733 mg. The colloidal gold curve was 14555555432. The sedimentation rate of the blood was 5 mm. in one hour. Complete blood counts and urinalysis revealed no significant deviations from normal.

A diagnosis of multiple peripheral neuritis with unusual characteristics was made. The girdle sensations, the feelings of constriction around the limbs, the involvement of the urinary sphincters, and the aberrant colloidal gold curve were suggestive of involvement of the nerve roots and possibly of the spinal cord. Hygienic measures, active and passive movements, and graduated physical activities were prescribed.

The patient continued to show steady and rapid improvement. By October 23 he was able to come to the office and to report that his hands "only tingle a little bit." His handwriting was much improved. The paresthesias in the lower limbs had receded to the feet. He still tired rapidly on walking up or down a staircase. About the middle of November he stated in a letter that his arthritis had recurred to an annoying degree. On December 5 he was free from paresthesias and weakness. At times he was bothered by twitching of the musculature of the arms proper. A complete neurologic examination on that date was negative in all essentials.

Discussion

The manner in which gold exerts its toxic effect is yet to be elucidated. Block and Knapp [4] have shown that oxygen consumption in vitro of slices of kidney and liver from healthy white rats which had received injections of gold is inhibited by the inorganic ionizable compounds, gold chloride and gold sodium thiosulfate, and uninhibited by the organic non-ionizable compounds, sodium succinimido-aurate, gold sodium thiomalate and gold thioglucose. They believe the inhibition is due to the presence of the gold ion in the reaction medium. They also state that the severity of the histopathologic changes in animals treated with gold is, in general, proportional to the quantity of gold laid down in the tissues.

Block, Buchanan and Freyberg [5, 6] studied the distribution of various gold compounds in the tissues of rats after intramuscular injection but did not include nervous tissue in their investigation. Steiner and Fischl,[7] however, found traces of gold in the brains of dogs after injections of Solganal, and in relatively large quantities in the gray matter of the brain of a patient who died from multiple sclerosis after having been treated with injections of gold.

Since accidents due to chrysotherapy have been observed after the use of various gold salts, it may safely be assumed that the gold, not the chemical combination in which it is included, is responsible. Hench [8] is of the opinion that, since most undesirable reactions occur after appreciable amounts of gold salts have been administered, they are probably due to metallic protoplasmic poisoning. The optimal dosage of gold salts has not yet been agreed upon.

According to Sundelin,[9] focal reactions are frequent during the course of treatment with gold. They occur most often after the first injection, are fleeting as a rule or last only a few days. While not so frequent as focal reactions, general reactions are of greater significance, since they may be precursors of serious complications. They comprise chills, fever, elevation of the sedimentation rate, fatigue, depression, headache, loss of appetite, transient albuminuria and the appearance of erythrocytes in the urine. These reactions may be considered indices of the sensitivity of the individual to gold preparations. Complications of all degrees of severity may involve the skin, the respiratory system, the mucous membranes of the buccal cavity, stomach and intestinal tract, the urinary tract, the blood, the organs of special sense and the nervous system.

Sundelin has shown that complications involving the nervous system are not infrequent and may be severe. When, as often occurs, they appear in conjunction with other more obvious untoward effects, they may be overlooked. He was able to collect 964 instances of complications, of which 107 involved the central nervous system. In most instances the symptoms suggested damage to the brain

and associated structures. Some 10 cases showed evidence indicative of involvement of the peripheral nerves alone.

In most cases, peripheral nervous involvement is accompanied by severe pain of boring, burning or lancinating type which is often paroxysmal in nature ("crises algiques transitoires"). It may be said that neurologic symptoms may range from the slightest to the most severe, and that they may arise from the brain, spinal cord, neural plexuses or peripheral nerves. The symptoms may be purely subjective, or may be characterized by epileptiform seizures, delirium and coma, or by transient or relatively persistent evidences of polyneuritis with paresthesias, weakness or paralysis of the limbs, loss of common and deep sensation, and diminution or loss of the superficial and tendinous reflexes. Vasomotor changes of transitory nature are frequent.

Among the 10 cases cited as involving the peripheral nerves there were four instances of herpes zoster, none of which was severe. One was preceded by dysphagia with nasal regurgitation and dysarthria. Another case occurred after the fourth injection of gold. The patient, a girl of 12, had developed an eruption and nephritis two years before after taking Solganal by mouth. During her second course of treatment she developed herpes zoster. A year after the herpes zoster she suffered from stomatitis after the ninth injection of a third course of treatment. One case of paresis of the left brachial plexus was observed. Three patients complained of paresthesias of the fingers and feet. The first patient of this group also developed an exanthem and protracted stomatitis; the second suffered from dizziness and alopecia over an area at the vertex as well as from paresthesia. Two cases showed loss of the sense of smell.

Lescher described the case of a woman who developed a clinical picture indistinguishable from acute infective polyneuritis with facial diplegia (syndrome of Guillain-Barré) after eight injections of Myochrysine.

Summary

A case of severe disabling polyneuritis which followed gold therapy for rheumatoid arthritis has been reported. The clinical findings were unusual. Recovery was rapid and complete.

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THORACIC STOMACH SIMULATING LEFT VENTRICULAR FAILURE *

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Introduction

Although the subject of diaphragmatic hernia has appeared in the medical literature with increasing frequency during recent years, it is still felt that not enough emphasis has been placed on it as a mimic of other abdominal conditions as well as of various cardiac and pulmonary diseases. Levy and Duggan [1] found 26 hiatal hernias in their series of 1,220 patients—an incidence of 2.1 per cent. Harrington [2] states that at the Mayo Clinic from 1926 through 1939, 650 patients were found to have diaphragmatic hernias. The actual incidence is probably greater than that reported because some patients with hiatal hernias are asymptomatic, and others, who do have symptoms, are not examined roentgenologically. Furthermore, the hernia may be missed either because the roentgenologist is not looking for it or because, as often happens with a small one, the hernia may not be demonstrable at that particular time.

In the adult, the most common type of herniation through the diaphragm occurs through the esophageal hiatus. Whereas herniation of small portions of the stomach through this hiatus is not uncommon, herniation of the entire stomach into the thoracic cavity, producing what has been popularly called an "upside down" stomach, is very rare. Ross,[3] of the Lahey Clinic, states that no completely thoracic stomachs have been seen there in the past six years, although smaller hernias are frequently encountered. Harrington [4] reports that of all the hiatal hernias seen at the Mayo Clinic, about 2.5 per cent show the complete stomach to be herniated. Schiff [5] of Cincinnati, although he gives no figures, states that he believes this condition to be very rare, and with this opinion Crohn [6] of New York is in complete agreement. Sussman [7] states that one or two such cases are seen each year in the roentgen-ray department of the Mount Sinai Hospital in New York.

Because of the rarity of this interesting situation, and to call attention to the difficulties which are encountered in its diagnosis, the following case is being reported.

* Received for publication June 1, 1948.

Case Report

This 71 year old female was first seen on February 16, 1948, at which time she complained of sudden episodes of severe difficulty in breathing of two years' duration. She stated that she had had stomach trouble "all her life." However, her earliest definite memory of such trouble dated back to the age of 24, when she had repeated episodes of pain across the upper abdomen associated with nausea. She became pregnant for the first time at the age of 29 and during this pregnancy, as well as during five subsequent ones, she always had nausea and heartburn. She did not remember whether these symptoms were worse during the last trimester of each pregnancy. After her last pregnancy she continued to have stomach trouble, manifested by nausea

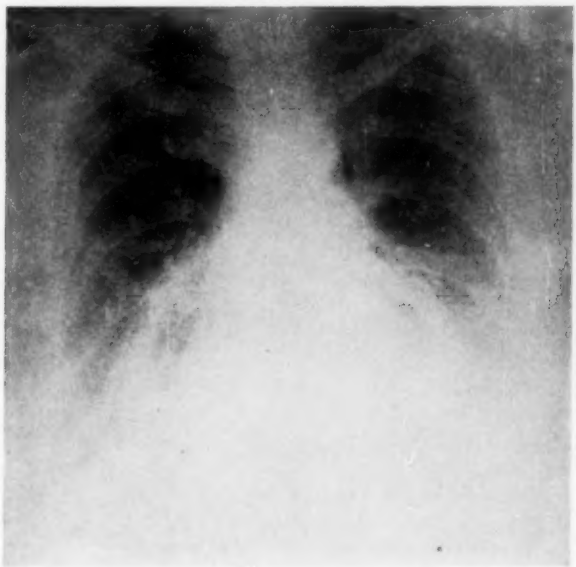

Fig. 1. Chest film showing stomach shadow around heart.

and increased belching, and relieved by bicarbonate of soda. There was no shortness of breath at any time. Two years ago, several hours after her noon meal, she was suddenly seized with a peculiar sensation in her head, associated with faintness and dizziness. She was then told for the first time that her blood pressure was elevated. The headache and dizziness continued for about one and one-half years and then gradually disappeared. After this episode she began having attacks of severe dyspnea associated with a sensation of heaviness in the chest. These attacks usually lasted one to two hours and then disappeared spontaneously. They were of very sudden onset and would usually come on after eating a heavy meal. She described them as a sensation of smothering or suffocation, with rapid, shallow respirations and rapid heart action. On many occasions she felt as though death was imminent. She discovered that she could get some relief by lying face down across the bed. She was treated by various physicians on the basis of hypertensive and arteriosclerotic cardiovascular disease until one doctor finally fluoroscoped her after a barium swallow. He told

her that part of her stomach was in her chest but that she was too old to be operated on. No films were taken at that time. He gave her some medicine which afforded her no relief. During the past year and a half, she has been worse in that her paroxysmal attacks of dyspnea have been more frequent and more severe.

Physical examination revealed a well developed, obese, 71 year old female who appeared younger than her stated age. Her weight was 180 pounds and she was 5 feet 4 inches tall. Examination of the fundi revealed slight narrowing of the arterioles. The neck veins were not distended. The lungs were clear to percussion throughout. The breath sounds were normal and no râles were heard. There were no gurgling sounds heard anywhere in the chest. Examination of the heart showed regular rhythm with normal heart sounds. No murmurs were heard. The apex beat was palpated five and one-half inches to the left of the midsternal line in the fifth interspace. The pulse was 84 and the blood pressure was 175/85 mm. Hg.

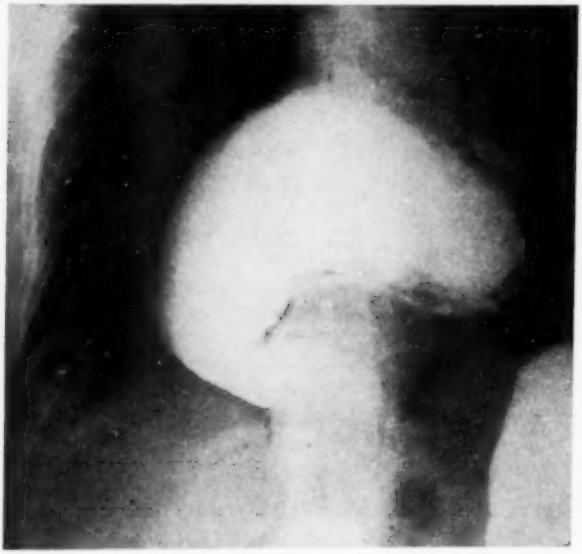

FIG. 2. Barium-filled stomach completely in the thorax.

Examination of the abdomen was done with difficulty because of her extreme obesity, but no gross masses were felt. The liver was not felt. There was no hepato-jugular reflux.

Urine examination was normal, as were the hemoglobin and blood count. Repeated examinations of the stool for occult blood were negative. A chest roentgenogram showed a peculiar domelike shadow on either side of the heart. This, in view of the findings of the barium meal, was determined to be the air-filled stomach (figure 1). The heart shadow appeared to be entirely normal. An electrocardiogram showed left axis deviation, a rate of 75 per minute, and no evidence of myocardial damage.

Barium enema revealed multiple diverticula throughout the large bowel, which was entirely beneath the diaphragm. After evacuation of the barium, air was introduced as a contrast medium but no further information was obtained.

A barium meal examination was then done. The esophagus appeared to be without evident lesion and there was no obstruction at its junction with the stomach. After leaving the esophagus, the barium, instead of proceeding downward, went upward into the thoracic cavity, filling the stomach, which was entirely in the thorax (figure 2). The greater curvature of the stomach was superior to the lesser curvature and both were smooth in contour, with no evidence of ulceration. The pylorus was on the right side and was just below the right diaphragm. At the end of five hours the stomach was empty. A lateral view showed the barium-filled stomach to be in the posterior mediastinum (figure 3).

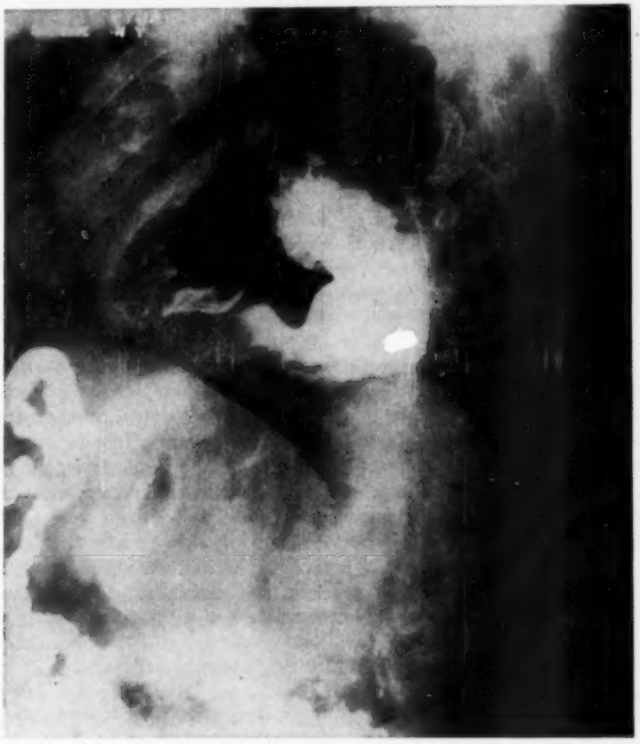

FIG. 3. Lateral view showing the stomach to be in the posterior mediastinum.

She was advised to eat small meals at frequent intervals and at no time to overload her stomach. Weight reduction was insisted on and, in addition, she was cautioned against lying down immediately after eating and was instructed to elevate the head of her bed six to eight inches. Trasentine with phenobarbital was prescribed.

In spite of faithful adherence to this regime she has continued to have episodes of paroxysmal dyspnea, although she does admit they have not been as severe. Because of the persistence of her symptoms operation was advised, but to date she has refused to undergo this procedure.

Discussion

Diaphragmatic hernias may conveniently be classified [8] as either traumatic or non-traumatic. The non-traumatic hernias may be further classified as congenital (present at birth) or acquired (developing through a congenitally weakened or deformed diaphragm).

Owing to the unusual embryologic formation of the diaphragm,[2] this structure may have weaker areas in different portions which account for the various types of hernias seen. The anterior, lateral and central parts, which comprise the larger part of the diaphragm in the adult, are formed from the transverse septum and fused ventral mesentery. The remaining, postero-lateral portion is formed by the fusion of the dorsal mesentery and the mesoderm derived from the receding wolffian body with the pleuroperitoneal membrane, derived from the pulmonary ridge. Failure of fusion or failure of proper deposition of the mesoderm at any of these points of union may result in a congenitally weak portion in the diaphragm. Thus, dorso-laterally are seen hernias through the foramen of Bochdalek; ventrally through the foramen of Morgagni and also through the esophageal opening. Hernias through the dome cannot be explained on this basis and are usually due to some pathologic process involving that area.

The question of the time of appearance of hernias of the diaphragm is not definitely settled. Truesdale [9] maintains that at the time of birth the stomach is below the diaphragm, but that immediately after birth, with the changed intrathoracic mechanics due to respiration, portions of the stomach may be drawn through the weakened areas in the diaphragm into the thoracic cavity. Harrington,[2] on the other hand, feels that while this way may be the explanation in some cases it by no means explains all cases. He believes a number are due to a congenital short esophagus which prevents the descent of the stomach into the abdominal cavity prior to the complete formation of the diaphragm. In other instances, a portion of the stomach fails to descend completely, even though a shortened esophagus is not demonstrated.

The symptoms of diaphragmatic hernia may begin at any time of life but usually, because these hernias have a tendency to become larger as the patient grows older, they first become apparent in the sixth decade. The usual complaints are abdominal pain, gaseous eructation, vomiting, severe dyspnea, hemorrhage, weakness, anemia, and palpitation. Most frequently symptoms come on immediately after eating a heavy meal, although even small amounts of food may precipitate an attack. The patients usually discover that lying down aggravates the symptoms, while sitting or standing affords some comfort. They may complain of a sensation of fullness and gaseousness with inability to belch. This, of course, is due to the trapping of air in the herniated portion of the stomach with spasm at the hiatal opening. Radiation of the pain is often noted, and pain between the shoulder blades, in either shoulder, and in the throat and jaw may be present. The symptoms may vary in different patients and there is no constant correlation to the size of the hernia. Some patients with large hernias may have no symptoms, while others with small hernias may have many complaints. In general, the symptoms will depend on the degree of mechanical interference with the function of the herniated viscera; on interference with the function of the diaphragm; on the amount of increased pressure in the thorax

causing impairment of the circulation and respiration; and on the severity of anemia.

The diagnosis on clinical grounds alone is very difficult and frequently is missed. Harrington [10] reports 295 cases with an average of three previous erroneous clinical diagnoses per case. The most common errors in order of frequency were: cholecystitis, cholelithiasis, gastric ulcer, duodenal ulcer, hyperacidity, secondary anemia, heart disease, carcinoma of the cardia, stricture of the esophagus, appendicitis, and intestinal obstruction.

Even the diagnosis of tuberculosis has been made, and patients have been treated for that disease for several years.[11, 12, 13] Aufses' case [11] was finally diagnosed when an attempted chest aspiration produced gastric contents. More uncommonly, the erroneous diagnosis of mediastinal tumor,[13, 14] hydropneumothorax,[12, 14] acute cor pulmonale,[15] and cardiac infarction [16] have been made. Small wonder that Harrington refers to diaphragmatic hernia as the "masquerader of the upper abdomen." [17]

Herniation through the esophageal hiatus especially is often mistaken for heart disease.[16, 18] In such hernias usually only the stomach is involved, although portions of the omentum as well as spleen may be included. The only symptoms complained of may be precordial pain radiating to the left shoulder and down the left arm. Harrington [17] believes these symptoms are caused by reflex constriction of the coronary arteries mediated through the vagus. Jones,[19] on the other hand, believes that the pain is mediated over the visceral afferent fibers supplying the esophagus and the cardiac and fundic portions of the stomach or over the sensory afferent fibers from the diaphragm, contained in the phrenic or middle or lower thoracic nerves. He is of the opinion that overdistention of the lower end of the esophagus or herniated portion of the stomach may cause typical anginal pains, and cites experiments in which distention of the esophagus by balloons caused such angina. Attacks of paroxysmal auricular tachycardia may be the presenting complaint of some patients. Our patient noted extremely rapid heart action during her episodes of dyspnea and this was an additional reason why heart disease was suspected. This patient exemplifies, too, the extreme dyspnea that may be present in some instances. After viewing the roentgenograms, one can understand how a thoracic stomach, distended either from food or gas, can so diminish the aerating capacity of the lung as to cause rapid, shallow breathing. Another factor in the production of the dyspnea is the interference with the venous return of blood due to the obstruction produced by a distended stomach.

It is of the utmost importance to differentiate heart disease from hiatus hernia. Truesdale, Hunt and Leigh [20] reported the case of a 38 year old male who died following perforation of an ulcer in the herniated portion of the stomach. Operation had been delayed too long because he was suspected of having myocardial damage and was considered too poor a surgical risk. Our patient presented herself with the chief complaints of dyspnea and tachycardia. When to that are added her age, her moderate hypertension, her fundus changes, and her obesity, it can be seen that the first impression would be paroxysmal dyspnea of cardiac origin.

The differentiation is made all the more difficult because the symptoms usually occur in the age group in which coronary disease is prevalent. A definitely abnormal electrocardiogram is of some help, but a normal one does not exclude

angina of coronary origin. From the standpoint of differential diagnosis, the size and type of the hernia are of little or no importance. Some help may be obtained from the fact that lying down may aggravate the discomfort of a hernia, while the opposite is true of angina pectoris. Then, too, while exertion almost always initiates the pain of coronary artery disease, it is not so constant a precipitating factor with hiatal hernias. In 25 patients with hiatal hernias, Jones [21] found eight who stated the pain was initiated by exertion but not constantly. Eight of the 25 also stated that they obtained relief with nitroglycerin, but in no case was relief as regular as with true coronary angina.

On finding a hiatal hernia, one should be careful not to attribute all such symptoms to it, as there is no reason why a patient cannot have coronary artery disease also.[22] Furthermore, the incidence of acute cholecystitis, appendicitis, or any other acute surgical or medical condition is just as high in this group of patients as in any other group.

Treatment

Treatment of these cases will depend mainly on the symptomatology and, on this basis, cases of hiatus hernia may be divided into three groups. In the first group are those patients who have no symptoms and whose hernias are discovered during a routine examination. Prevention of obesity is all that is required for this group except in those cases where anemia secondary to bleeding is present. It may be necessary to operate if the bleeding is persistent and severe.

The second group would be comprised of those patients whose symptoms are moderate and whose hernias are generally of moderate size. These patients will usually respond to smaller feedings given at more frequent intervals, to anti-spasmodics, and to elevation of the head of the bed, in addition to dietary control in the prevention and treatment of obesity. These patients do better if they are not emotionally upset and tense. In this respect, patients with hiatal hernias are similar to ulcer patients in that symptoms may be initiated or aggravated by emotional trauma.

In the third group would be those patients who do not respond to the conservative management outlined above. In these cases the hernias are usually very large. Harrington [2] is of the opinion that, in all cases where one-third or more of the stomach is involved, operation should be considered, because the condition is progressive and usually the progressive enlargement becomes more rapid after the hernias have attained this size. In all cases in which the colon is involved, operation is necessary because of the danger of intestinal obstruction. Traumatic hernias and those in which there is a congenital absence of a portion of the diaphragm should be treated surgically, because the colon and small bowel are usually involved and the incidence of intestinal obstruction is high.

Conclusions

An unusual case of diaphragmatic hernia with symptoms mimicking left ventricular failure is presented.

Attention is called to the difficulties frequently encountered in making the correct diagnosis.

This condition must be ruled out in all patients whose symptoms simulate heart disease and in whom no positive evidence of such condition can be found.

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LOWER NEPHRON NEPHROSIS ASSOCIATED WITH PULMONARY INFARCTION *

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THE occurrence of lower nephron nephrosis with pulmonary infarction has not, to our knowledge, been previously reported. It is the purpose of this report to add pulmonary infarction to the list of etiologic factors in lower nephron nephrosis. The evidence presented leaves little doubt that it was the cause of the renal lesions which precipitated the death of the patient.

CASE REPORT

A 55 year old white male farm laborer was admitted to the hospital on February 21, 1947. His chief complaint was pain in the left chest of four days' duration.

The present illness had begun one month earlier, at which time he had first noted some swelling of the right ankle. Sharp knife-like pain in the left chest and dyspnea appeared four days before entry. There was no history of fever or hemoptysis.

The past history revealed that the patient was a periodic drinker. In 1942 he had been hospitalized for the treatment of hypertension and nephritis. The findings on admission were albuminuria and hematuria. Subsequent urinalyses and renal function tests were normal. His blood pressure ranged from 198 mm. Hg systolic and 100 diastolic to 154 systolic and 86 diastolic. He was discharged as improved and reported no further urinary or cardiac symptoms. The family history was noncontributory.

On admission to the hospital, the patient appeared acutely but not seriously ill. He was well-nourished and well-developed. There was no evidence of orthopnea, cyanosis or icterus. The temperature was 100° F., the pulse rate 88, and the respiratory rate 22. The blood pressure was 160 systolic and 90 diastolic. The excursions of the left chest were restricted. Percussion was impaired, breath sounds were absent, and a friction rub was heard over the lower left chest. The remainder of the examination was negative except for a slight degree of pitting edema of both lower extremities.

On admission, the hemoglobin was 8.5 gm., the red blood cell count 2,670,000 per cu. mm., the white blood cell count 5,200 per cu. mm., with 82 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, and 6 per cent monocytes. Urinalysis was normal. The blood Wassermann and Kahn reactions were negative. A roentgenographic examination of the chest revealed pleural haziness at the left base and slight elevation of the left diaphragm. An electrocardiogram was reported as being within normal limits.

Penicillin therapy was instituted on the day of admission. Symptomatic improvement and return of temperature to normal followed within one week. Because of the previous history of hematuria and diagnosis of nephritis, the genito-urinary system was investigated. Repeated urinalyses were normal. The specific gravity of the urine ranged from 1.009 to 1.018. A urea clearance renal function test was

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100 per cent of normal. The nonprotein nitrogen was 37 mg. per 100 c.c. The total serum protein was 7.5 gm., with a normal A/G ratio. The cephalin-cholesterol flocculation test was negative, and the icterus index was 10. Prothrombin time was 100 per cent of normal.

By April 5, the red blood cell count had risen to 3,470,000 per cu. mm., with a hemoglobin of 11.0 gm. That afternoon the pulse rate suddenly increased to 100 and the respiratory rate to 24. The following morning the patient complained of severe, sharp, stabbing pain in the right chest on inspiration. His temperature rose to 100.8° F. Auscultation of the heart revealed a basal gallop rhythm and accentuation of the pulmonic second sound. There was marked splinting of the right chest. A dull per-

FIG. 1. Kidney, gross. Enlarged, pale-tan, sharp differentiation between cortex and medulla.

cussion note, diminished breath sounds, and a pleural friction rub were heard over the right lower chest. A roentgenogram of the chest showed marked elevation of the right diaphragm with increased density in the right base. On April 7 he began to vomit. Two days later jaundice appeared. Thrombosis of the left saphenous vein was detected on April 9, and the left femoral vein was ligated. At the same time Dicumarol therapy was instituted, and two days later the prothrombin time was reduced to 36 per cent of normal. Oliguria appeared on April 12. The following day he vomited a considerable amount of coffee-ground material and his urine became grossly bloody. At this time the hemoglobin was 6 gm., the red blood cells 1,900,000 per cu. mm., and the prothrombin time 30 per cent of normal.

Dicumarol was discontinued and the patient was given 72 mg. of vitamin K intravenously because of uncertainty as to the nature of the bleeding. This was followed by two transfusions of whole blood. The following morning the patient was confused and presented muscular twitchings. The prothrombin time was 40 per cent

of normal; carbon dioxide combining power of the blood was 33 vol. per cent; blood chlorides 462 mg. per cent; blood nonprotein nitrogen 171 mg. per cent, and creatinine 30 mg. per cent. During the next 24 hours the patient voided only 150 c.c. of smoky or bloody urine, and his blood pressure rose to 186 systolic and 90 diastolic. On April 15 he suddenly died.

A review of his treatment shows that the patient received a total of 3,240,000 units of penicillin, 800 mg. of Dicumarol, and 2,500 mg. of Demerol. He was given 500 c.c. of whole blood on April 13 and 14, and parenteral fluids daily.

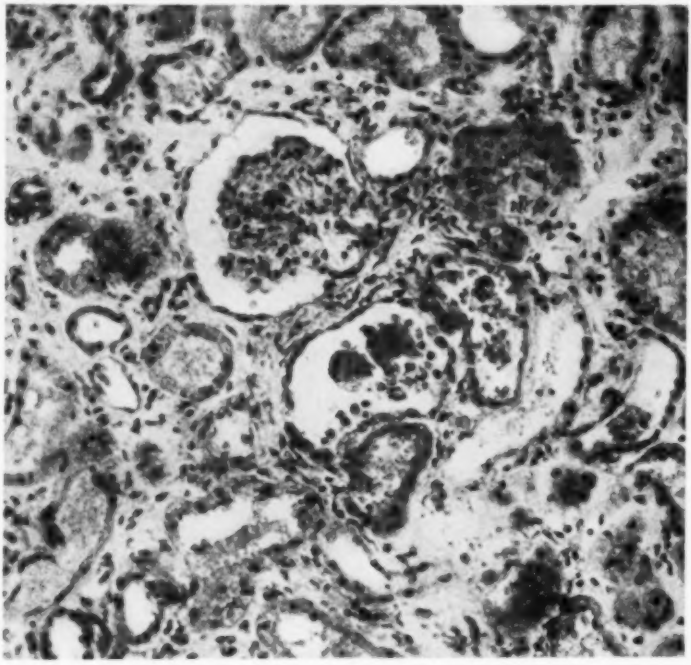

FIG. 2. Kidney photomicrograph (high power). Degenerative changes of distal tubules, "heme" casts in a dilated tubule; interstitial tissue shows edema and inflammatory cells; glomeruli intact.

Necropsy was performed 16 hours after death. In the left inguinal region there was evidence of a recent femoral vein ligation. No edema of the face or extremities was seen. The subcutaneous tissue, however, was edematous. The peritoneal cavity contained about 750 c.c. of straw-colored fluid. The intestines were distended. Each pleural cavity contained about 1,200 c.c. of straw-colored fluid.

Lungs: In the lower portion of the left upper lobe there was a wedge-shaped scar with an overlying fibrous pleurisy. In the right lower lobe there was a recent hemorrhagic infarction measuring 5 by 3 cm., overlaid with a fibrinous exudate. A thrombus occluded a stem pulmonary artery at the hilus of this lobe. Within the left femoral vein, residuals of the thrombus which caused the pulmonary infarction were found.

Heart: The heart weighed 250 gm. The myocardium was firm, indistinct, moist, and light-brown in color.

Kidneys (figure 1): Both kidneys were considerably enlarged, the right weighing 300 gm. and the left, 325 gm. Upon stripping the capsule, a finely granular, pale-tan surface was exposed. Upon section the kidneys were found to be swollen. The surface markings were unusually distinct, the pale-brown cortex being sharply differentiated from the gray-brown streaked pyramids. The tips of the pyramids showed hemorrhagic linear streaks with erosions of the papillae. The mucosa of the pelvis showed pin-point hemorrhages. Within the pelvis there were blood clots. The walls of the ureters were edematous.

Microscopic Examination. Lungs: A section from the left upper lobe showed fibrous tissue with an old, organized thrombus. Section from the right lower lobe showed hemorrhagic infarction.

Kidneys (figure 2): There was evidence of minimal arteriolosclerotic nephrosclerosis. The glomeruli were slightly enlarged. The distal tubules showed marked destructive changes. Hyaline and "heme" casts and occasional erythrocytes were found within the distal tubules. The epithelium of these tubular structures was undergoing considerable degenerative changes. In places, epithelial cells were desquamated, and others were deep-blue in color. Buds of epithelial tissue either projected into the lumen or herniated into the interstitial tissue. Giant cells were formed by these structures, notably about the "heme" pigment. Within the interstitial tissue there were inflammatory changes characterized by foci of edema, lymphocytes, monocytes, polymorphonuclear cells, and rarely eosinophilic cells. The blood vessels showed no marked changes. Stained with sudan IV, the tubules showed minimal fatty degeneration. The "heme" casts within the distal tubules failed to take the Dunn-Thompson [20] stain for hemoglobin.

Anatomic Diagnosis: Old infarction of left upper lobe; recent hemorrhagic infarction, right lower lobe with pleurisy; thrombosis of left femoral vein; ascites, hydrothorax, anasarca; paralytic ileus; acute toxic nephrosis.

Microscopic Diagnosis: Lower nephron nephrosis.

Cause of Death: Lower nephron nephrosis; infarction of lung due to embolus from thrombosis of left femoral vein.

Discussion

The renal lesions in this patient were typical of lower nephron nephrosis. In an authoritative study and report of 538 cases, Lucké [1] first used the term in preference to crush syndrome, transfusion nephrosis, hemoglobinuric nephrosis, and a host of other names, inasmuch as they have common clinical features and demonstrate a unique and characteristic location of the renal lesions. The most common causes of this condition are crushing injuries, battle wounds, abdominal operations, incompatible blood transfusions, sulfonamide intoxication, blackwater fever, heat stroke, retroplacental damage and eclampsia, hemolytic anemia, alkalosis, and certain poisons. The characteristic lesion is confined to the thick tubules of Henle and distal convoluted tubules which show degeneration or actual necrosis invested by interstitial edema, pigment casts within the tubules, and little or no alteration of the glomeruli and proximal tubules. Clinically, the syndrome is commonly manifested by prodromal symptoms of shock and vomiting. Oliguria or anuria, hematuria, azotemia, hypertension, occasionally edema and, finally, uremia occur within a few hours to 10 days. The mortality rate is apparently high and the duration of the disease usually a few to 10 days.

Opinions as to the nature and cause of this syndrome vary and have been the subject of numerous pathologic studies. Hemoglobin precipitation, blockage of renal tubules by "heme" pigments, renal anoxia, reflex renal ischemia, shock, electrolyte imbalance, and toxicity of certain products of hemoglobin or myoglobin are the many factors which at one time or another have been implicated as the cause of the renal change. For detailed discussion of the pathogenesis of lower nephron nephrosis, the papers of Lucké, Flink and others may be consulted.[1-14]

In this case, the question arises as to whether the pulmonary infarction and lower nephron nephrosis were concurrent or specifically related conditions. Transfusion nephrosis need not be considered, since oliguria and hematuria preceded the administration of blood. The only possible incriminating drugs used were Dicumarol and Demerol, neither of which has been known to cause lower nephron nephrosis.[16, 17, 18, 19] The presence of alkalosis was not noted during this hospitalization.

The clinical course suggests a specific relation, inasmuch as hemorrhagic infarction of the lung, with abrupt fall in the red blood cell count and sudden appearance of vomiting and icterus, was followed by oliguria, hematuria, azotemia, and uremia. The distinct pathologic renal lesions found at autopsy fulfill the criteria of Lucké for the diagnosis of lower nephron nephrosis.

The mechanism of production here may be similar to placental hemorrhagic infarcts causing toxemia. Young [14] proved experimentally that autolytic products of a necrotic infarct of the placenta would produce degenerative changes in the convoluted tubules of the kidney. Paxson [15] reported three obstetrical cases with urinary suppression, one of which showed bloody extravasation and infiltration into body tissue as a result of a twisted ovarian cyst. He proposed that the infiltration of the blood into the tissue probably released a toxin causing the characteristic renal lesion, and felt that other hemorrhagic conditions may act in a similar fashion. In the case we present it seems probable that the release of either some toxic autolyzed substance or hemoglobin derivative product from within the infarction of the lung in the presence of previously damaged kidneys was responsible for the development of the renal lesions which caused the death of the patient.

Summary

A case of lower nephron nephrosis associated with pulmonary infarction is reported. The report indicates that pulmonary infarction may possibly be added to the known list of etiologic factors causing lower nephron nephrosis. The precipitating factor was apparently absorption of toxic or hemoglobin derivative products resulting from the pulmonary infarction.

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CARDIAC FAILURE IN A "NORMAL" HEART *

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SOME time ago a man died in Strong Memorial Hospital in Rochester, New York, with a provocative clinical history and postmortem findings. The man had enjoyed excellent health until his last five or six years, when there were signs and symptoms of cardiac insufficiency. He finally died in decompensation. At postmortem examination, however, his heart was anatomically normal.

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Case Report

The patient, a white man aged 51 years, was admitted to the Rochester General Hospital on May 17, 1936. His chief complaint was of a hernia in the inguinal region. He stated that his general health had always been good, but in system review he admitted moderate dyspnea unassociated with cough, hemoptysis, pain, or peripheral edema. His appetite was good, his bowels were regular, and he denied indigestion. He was a well-developed, obese man in no difficulty. His blood pressure was 130 mm. of mercury systolic and 80 mm. diastolic. His pulse rate was 80 beats per minute and respiration was 20 per minute. A few moist râles were heard over the left lung posteriorly, but otherwise nothing abnormal was found in the thorax. The heart could not be well outlined. The sounds were distant, and no murmurs were heard. The pulse was full and regular. No peripheral edema was noted. Examination of urine revealed nothing abnormal, with a specific gravity of 1.010. The blood Wassermann reaction was negative for syphilis.

A Bassini hernioplasty was done, with removal of a hernial sac which was the size of a walnut and contained some fat tissue but did not give evidence of inflammation. The operation was done under ether anesthesia and was uneventful and without sequelae. The patient was discharged on the seventeenth postoperative day.

In 1938, two years later, he was admitted to Strong Memorial Hospital with complaints of chills, fever, and hemoptysis of four days' duration. He was now 53 years old, and had been in good health until the onset of these complaints. Coincident with the chills he had noted a sudden, sharp, nonradiating precordial pain which did not persist. His cough became more severe and, the day before admission, productive of blood-tinged sputum. His temperature started at 102° F.; he became dyspneic, was unable to sleep, and developed marked anorexia with vomiting. Abdominal distention was noted from the onset, and enemas were necessary for the constipation. On admission he complained of pain in the right upper part of the chest anteriorly. The patient stated that he had suffered from shortness of breath with precordial pain on exertion for the past few years. He had found it necessary to inhale "spirits of ammonia" when climbing steps. Otherwise his general health was good. There was no history of diphtheria, rheumatic fever, or syphilis. He admitted gonorrhea without sequelae at the age of 20 years.

His father had died at 91 years of throat cancer, his mother at 84 years of heart disease. Two brothers died of pneumonia at eight and one-half and 23 years, respectively. Two sisters were living and well, and one brother was living but had stomach trouble. There was no history of tuberculosis, diabetes, gout, nervous, mental, allergic, or kidney diseases in the family.

Physical examination revealed an acutely ill man, with a persistent cough productive of blood-tinged, mucoid sputum. He was propped up in bed but gave no evidence of cyanosis, icterus, or peripheral edema. The temperature was 39.8° C., pulse rate was 75, and blood pressure 110 mm. systolic and 80 diastolic.

The following significant findings were noted: The fundi showed well outlined disks and no papilledema. The vessels were of normal caliber, and no hemorrhages or exudates were noted. The thorax was thick and obese; expansion was bilaterally equal, and without splinting. Tactile fremitus was increased, and the percussion note was dull over the upper part of the chest on the right, posteriorly. Some impairment of the percussion note was noted low on the left side of the chest, posteriorly, where there were patchy signs of consolidation. Whispered voice was increased, and tubular breathing was apparent over the right middle and upper lobes, posteriorly.

Percussion of the heart disclosed the left border of cardiac dullness 10.5 cm. from the midsternal line in the fifth interspace. The right border was retrosternal. There were no shocks or thrills, but the sounds were of poor quality and without murmurs. The rhythm was totally irregular, with a definite pulse deficit.

The abdomen was obese and slightly distended, and no organs or masses were palpable. Costovertebral tenderness was noted bilaterally. Rectal and neurologic examinations disclosed nothing significant.

The laboratory studies on the blood included a leukocyte count of 18,700 per cu. mm., with 88 per cent neutrophils; erythrocyte counts of 5,850,000, and a hemoglobin of 17.2 gm. per 100 c.c. The cellular morphology was normal. The urine showed a specific gravity of 1.020, was acid, contained albumin graded 2 plus, and was negative for sugar, acetone, and blood. Microscopic examination showed a few granular casts and an occasional leukocyte of the centrifuged specimen. Examination of urine before dismissal from the hospital gave completely negative results. Stool examination revealed nothing of significance. There was 44 mg. of nonprotein nitrogen per 100 c.c. of blood, and the plasma chloride level was of 96 milliequivalents (564 mg. per 100 c.c.). Blood culture was strongly positive for type I pneumococcus, but the sputum did not type specifically.

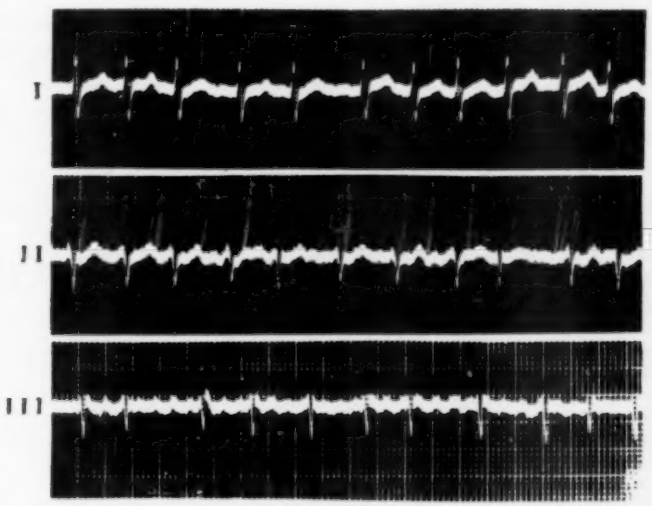

FIG. 1. Electrocardiogram taken during episode of pneumonia at the time of patient's first acute cardiac failure.

Roentgenologic examination of the thorax was interpreted as follows: "There is a diffuse, heavy density in the right upper lung field which comes just below the third rib anteriorly. The hilus and bronchovascular markings below that area are markedly accentuated. The heart is definitely enlarged with left ventricular predominance, but its contours are smooth and rather well rounded, which militates against specific cardiac pathology."

In the following five days the patient received more than 1,200,000 units of type I antipneumococcal serum, and his temperature responded satisfactorily. On the afternoon of the second day in the hospital, his heart sounds were poor in quality and of an irregular rhythm, and pulse deficit increased. Respirations were increased, expiratory wheezes were present, and coarse râles were audible at the bases of both lungs. A diagnosis of cardiac decompensation was made. An electrocardiogram taken at that time showed auricular fibrillation, slurred QRS complexes, and a low T wave in Lead III (figure 1).

On the basis of these findings, rapid digitalization with 19 c.c. of digitalone (extract digitalis leaves) within 24 hours was achieved. The pulse deficit disappeared and the response to the digitalis was apparent. During the next two days the patient's condition improved, the thoracic condition cleared, and the heart sounds were of better quality. The blood pressure then was 120 systolic and 80 diastolic. Mild hemorrhagic dermatitis with joint pains appeared 13 days after admission but this disappeared rapidly.

He was dismissed on the twenty-fifth day of hospitalization and instructed to continue to take 0.1 gm. of digitalis daily. He was checked periodically by his physician, Dr. A. F. Bastian. One month later, use of digitalis had been discontinued and the patient's activities were limited to office work and the use of the elevator at all times. His weight was recorded at 278 pounds (126.1 kg.). Four months after dismissal from the hospital the patient was seen because of an episode of acute bronchitis. He was not taking digitalis. His cardiac rhythm was regular, and the blood pressure was 160 systolic and 85 diastolic.

In 1939, one year after discharge from the hospital, the patient was seen at home in connection with treatment of his wife for an accidental injury. He was somewhat disturbed and complained of dyspnea and precordial pain brought on by the excitement of his wife's injury.

He was again examined for an episode of acute bronchitis four months later, in 1940. On that visit his blood pressure was 140 systolic and 84 diastolic, the cardiac rhythm was regular, and his weight was 224 pounds (101.6 kg.).

On June 24, 1942, the patient was readmitted to Strong Memorial Hospital complaining of intermittent diarrhea of 10 months' duration. Episodes of constipation had alternated with periods in which he had eight to 10 loose, watery stools daily. These occasionally were pencil-sized and streaked with blood. He had lost 50 pounds (22.7 kg.) in the last 10 months, but his appetite on a mild reduction diet remained good. Interval history since the last admission was not significant.

Systemic review was as follows: Head, eyes, ears, nose, and throat were free of symptoms. The patient suffered from shortness of breath with precordial pain on exertion, and on climbing steps required inhalation of ammonia. There were no bouts of paroxysmal nocturnal dyspnea, orthopnea, or edema. He had a chronic cough, but no morning cough, night sweats, or pleural pain. His appetite was always good, intake of food was ample, and he had no dietary idiosyncrasies. Occasional gaseous disturbances and some abdominal cramps bothered him, especially with his present complaints. Hematemesis and jaundice were never noted. There was nothing significant with regard to the genito-urinary and neuromuscular systems.

On physical examination no cyanosis, dyspnea, pallor, or orthopnea was noted. His temperature was 37° C., pulse rate was 76, respirations were 18, and blood pressure 118 systolic and 64 diastolic. The ocular fundi were negative. The nasal mucosa was erythematous, but the airway was patent. A tracheal shift to the right without a tug was recorded. The anteroposterior diameter of the thorax was increased, but the pulmonary fields were clear to percussion and auscultation. It was difficult to outline the heart by percussion because of the large thorax. No thrill was palpated. Cardiac rhythm was regular, the tones were distant but of fair quality, and no murmurs or extraneous sounds were heard.

The abdomen was soft and flat, with the question of a mass in the right upper quadrant noted. The sigmoid and descending colon were palpable in the left lower quadrant. On rectal examination, the sphincter tone was found to be good, and the prostate normal in size but tender to palpation. There was no peripheral edema, and the reflexes were physiologic throughout.

Examination of the feces disclosed occult blood. Roentgenologic examination after a barium enema showed a filling defect low in the sigmoid region.

On his eighth hospital day a combined abdominoperineal resection of the bowel was performed for removal of carcinoma presumably without any metastasis. Before operation his blood pressure was 120 systolic and 70 diastolic, and a few extrasystoles were noted. Lungs were clear. During the operation, which lasted six and a half hours, 1,100 c.c. of sodium chloride in 0.9 per cent solution, 500 c.c. of whole blood and 200 c.c. of plasma were given. At the end of surgery his condition was fairly good.

Twelve hours after operation pulse had climbed from 95 to 145 and was totally irregular with a pulse deficit. It was of fair quality, even though rapid. The patient showed marked wheezing and an increase in sputum, with respirations of 32 to 40. His color was dusky. Over the entire thorax, and especially at the bases, wet râles were heard. No definite sacral or peripheral edema could be found but the conjunctivae were definitely edematous. The abdomen was soft and the wound in good condition.

He was treated with oxygen, digitalis, and blood transfusions. The urine contained leukocytes, casts, albumin, and erythrocytes. The leukocyte count was 26,000 per cu. mm. of blood. Sulfadiazine was administered and a level of 15.7 mg. per 100 c.c. of blood was reached. Quinidine was given for three days without much effect. No other drugs were used. The concentration of nonprotein nitrogen was elevated to 72 and then to 98 mg. per 100 c.c. of serum. His course was gradually downward, and compensation of his circulatory system was never fully regained. He died eight days after the operation.

Necropsy. Necropsy was performed on July 10, 1942, by Dr. Frank Mann. On incision, 2 to 3 cm. of yellow fat covered the anterior abdominal wall, and the peritoneal surfaces were smooth and glistening, with some old fibrous adhesions beneath the herniorrhaphy scar. A few dense pleural adhesions were present on each side and the pericardial cavity was smoothly lined. No excess fluid was present in any of the body cavities.

The heart weighed 330 gm. The epicardial surface was smooth, and the anterior surface of the right ventricle was covered by normal-appearing yellow fat, varying in thickness from 2 to 5 mm. The endocardium was smooth and none of the chambers was dilated. The circumference of the valves was as follows: tricuspid 12 cm.; pulmonic 7 cm.; mitral 10.5 cm., and aortic 6.5 cm. The leaflets were thin and delicate without thickening and the chordae tendineae were delicate without fusion. The left ventricular wall measured 1.3 cm. in thickness and the myocardium was firm and red without evidence of scarring on numerous cross and tangential sections. The right ventricular wall measured 3 mm. on the average, but only about 2 mm. at the apex. The coronary arteries were of normal caliber and presented a smooth intimal surface throughout.

The left lung weighed 350 gm. and the right 450 gm. The left lung was pink, with moderate black pigmentation, and was crepitant and contained air, except for a zone of marginal congestion and edema posteriorly which measured 2 to 13 mm. in thickness. The bronchi presented pale mucosal surfaces and contained no secretion. The pulmonary arteries presented smooth intimal surfaces. The right lung was similar except that it showed a larger congested zone posteriorly.

The abdominal viscera were normally disposed and all suture lines were intact. Cloudy swelling and congestion of the spleen, liver, and kidneys were noted. The bowel was moderately distended and there were areas of acute serosal exudation on the portions adjacent to the pelvis. The kidneys were brownish and firmer than normal. The capsules stripped with ease, leaving a smooth surface. The cortex measured 1 cm. in thickness and the glomeruli appeared as small red dots. Striations were distinct and pyramids regular and normally arranged. The pelves and ureters were smooth and showed moderate submucosal injection.

The bladder showed a thickened indurated wall and some mucosal injection. On the posterior external wall was some acute exudate resembling that seen on the wall of the small bowel. The prostate was normal in size, consistency, and color.

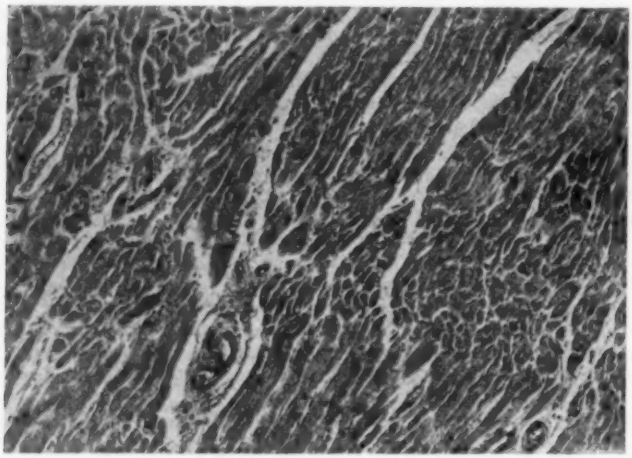

FIG. 2. Left ventricular wall (hematoxylin and eosin, × 100).

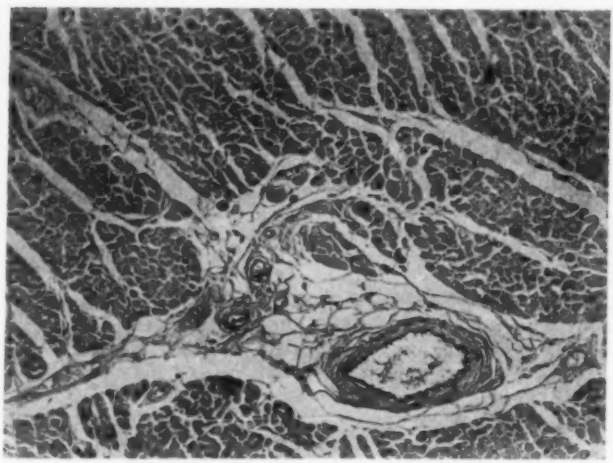

FIG. 3. Microscopic appearance of the right ventricular wall (hematoxylin and eosin, × 100).

The aorta was of normal caliber, with an elastic wall and a few small flat yellow atheromatous plaques on the intimal surface. The major arteries and veins were normal.

Microscopically, the epicardium of the left ventricle was thin and the underlying fat was normal in appearance. The coronary vessels showed slight intimal

thickening. The myocardium consisted of normal-appearing fibrils, with no evidence of inflammation or scarring (figure 2). The endocardium was thin, and a few areas of fat deposition were noted around the subendocardial vessels. The right ventricle presented a similar picture with no discernible microscopic abnormality (figure 3).

The lungs showed patches of pneumonia in different stages of development. The alveoli contained many erythrocytes and numerous polymorphonuclear leukocytes. Some alveoli contained only inflammatory cells and some showed organization. Polymorphonuclear cells were found in the small bronchi. A moderate number of macrophages containing pigment were present. In one section a few small pulmonary emboli were seen in the smaller vessels.

The kidneys showed an occasional hyalinized glomerulus, but the great majority of the glomeruli were normally tufted and not unusual. The tubules were well preserved and patent. There were a moderate amount of peripelvic fat and some increased submucosal fibrosis beneath the intact normal-appearing pelvic mucosa.

The final anatomic diagnosis was as follows: localized pelvic peritonitis; small pulmonary emboli; early bronchopneumonia; moderate bilateral pulmonary edema; fibrous pleurisy, and duodenal diverticulum.

Comment

The findings in this case suggest a problem in the diagnosis of the patient's cardiac disease. That he had decreased cardiac reserve cannot be denied. There were signs of this for years on exertion (climbing stairs), emotion (his wife's accident), the load of the pneumonia and, finally, the strain of the operative procedure. Yet, after all but the last episode, there were periods of complete compensation, which would indicate no lasting structural damage. Nor was any such change found at postmortem examination.

There was no evidence that dietary insufficiencies, hormonal disturbances, or hypertensive factors were effective to induce failure. Although the systolic pressure was recorded once at 160 mm. in his doctor's office, the diastolic was never elevated and he could hardly be considered to have hypertension. The lack of clinical evidence of valvular or myocardial damage in the intervals between episodes of failure raised a doubt as to the degree, if any, of permanent structural damage.

The patient was large, and obesity is known to place a strain on any normal sized heart. One can only conjecture as to why there was not the usual compensatory hypertrophy. Without the hypertrophy we cannot lay blame, as is customary, on the postulated failure of the circulatory supply to keep pace with the muscular enlargement.

Although the patient had the signs and symptoms of angina pectoris, there were none of the usual postmortem findings of arteriosclerosis. The fibrillation might suggest hyperthyroidism or some area of infarction, but no anatomic evidence was found for either condition. Furthermore, the symptoms of cardiac insufficiency were independent of the episodes of fibrillation. Of course, it is possible that an area of infarction escaped detection. Not enough microscopic sections were examined to rule out scarring entirely, but that is an ever-present objection for, regardless of technic, it is next to impossible to make a complete microscopic examination of the heart muscle.

Since this case does not fit easily into any of the formal classifications of heart disease, we would like to consider the possibility that it is an example of cardiac failure caused by inadequate musculature, per se. It seems possible in this case

that the inability of the heart to meet the demands of the emotional and physical exertion, the pneumonia, and the surgery should be attributed to the heart muscle itself.

Clinically, circulatory decompensation due to limited muscle strength is seen frequently. There are several different types, the first of which is seen when intravenous fluids are given too vigorously. That a perfectly normal heart can fail under such an overload is well known.

A second example of failure as a result of muscle weakness is seen when a mechanical obstruction suddenly alters the circulatory balance. This can occur with varying degrees of ruptured leaflet. The pump in such an emergency suddenly becomes an inefficient mechanical organ. Death may be prompt but, strangely enough, the patient occasionally lives for some time, even years. In two cases of equal severity, the difference between death in one and compensation in the other is the degree of reserve, or muscle strength, to meet the mechanical change.

The third type occurs in deficiency states associated with heart failure. Decompensation is overcome by physiologic means, thiamine chloride, thyroid hormone, and so forth. None of these seems to affect the heart anatomically, but rather to improve metabolism of the failing muscle.

Evidence of a fourth type is demonstrated in the present treatment of decompensation. Most of the measures act only on the muscle and its circulatory overload. Digitalis, venesection, or its counterpart the Danzer Apparatus, serve either by stimulating the muscle or by reducing the work load by decreasing the volume of blood. The effectiveness of diuretics is also thought to be along this line, all of which aims to increase cardiac efficiency without anatomic effect.

The classified etiologic factors of heart failure, at present, do not include inadequate musculature as a primary etiologic factor, except in a few deficiency states, such as deficiency of thiamine chloride or thyroid. Weakened muscle is usually considered as secondary to such factors as circulatory anoxia, inflammation, toxic states, valvular incompetencies, and similar difficulties. These classifications have derived their structure from the pathologic anatomist, who has been successful in demonstrating structural or inflammatory changes in most cases of heart failure. However, the physiologist has long maintained that clinicians are concerned too much with the apparent pathologic changes and not enough with the functional aspects of tissue.

The pathologic anatomist and, in turn, the classifications of heart disease, do not answer all the questions. For example, why is it sometimes years from the time that structural damage is accomplished before the so-called rheumatic heart fails? As Dock [1] has said: "It is a remarkable paradox that elevated arterial pressure or scarred valves which cause no difficulty even with a vigorous life at the age of 20 should be blamed for cardiac failure a few decades later when, due to falling basal metabolism and decrease in physical activity, the physical work of the heart is much less."

In another case, in which myocardial scarring is evident, failure and death may be attributed to myocardial infarction. This interpretation may be correct, for there is no doubt that at one time coronary insufficiency existed. But the evidence of healing after such damage is not enough by itself to explain the decompensation in all cases, especially when that heart has been able to carry its load for years with that scarred myocardium.

Furthermore, the presence of moderate amounts of atherosclerosis in the coronary vessels does not necessarily prove that those vessels were incompetent, even though the heart did fail. It is circumstantial evidence at best, and coexistence does not prove relationship. It is not uncommon, in cases of intermittent cardiac failure, to find at necropsy that the coronary vessels are sclerosed, a condition, however, which obviously must have been there for months or years. Such hearts are said to have failed from arteriosclerotic or coronary disease. Many undoubtedly do, but it is difficult to understand just how that permanent arteriosclerosis and its effect on the blood supply to the myocardium were reversible enough to allow long periods of compensation to follow the intermittent episodes of cardiac failure. It becomes even more confusing when we realize that such improvement is usually associated with a muscle "stimulant," such as digitalis. Yet it is said, from the anatomic appearance of the heart, that failure was due to arteriosclerosis.

We know, of course, that anoxia which results from sclerotic vessels has a profound effect on the efficiency of the musculature. But if acute or sudden occlusion does not occur, the determining factor of cardiac failure rests in the muscle itself and, therefore, not always in the vessels and their degree of sclerosis. It seems from the examples cited that change in the musculature itself may control the timing of heart failure in some cases. Such a change may be a physiologic one not demonstrable as yet by our present methods of examination, most of which are anatomic.

Finally, it may be postulated that alteration of muscle physiology in the process of aging may have more to do with failure in a case like the one reported than is generally recognized. A survey of records of 10,000 necropsies at Strong Memorial Hospital disclosed that, in the cases in which patients were more than 60 years of age and did not have systemic disease which might affect the heart, such as carcinomatosis, tuberculosis, hypertension, diabetes, and so forth, only 17 could be considered without anatomic change in the heart or coronary vessels of some sort. Such ratios have left little room for the pathologist to suspect failure of the myocardium from anatomic observation only. It is becoming increasingly apparent that what may be merely associated anatomic findings should not be relied on to form the basis for the diagnosis of a physiologic phenomenon. This is especially true in the older patient dying of heart failure.

Definite physiologic changes are being demonstrated with increasing frequency in the heart as it ages. Alterations of cardiac output,[2, 3] cardiac index, oxygen consumption,[4] response to drugs, heart tones,[5] pulse rate,[6] electrocardiographic findings,[7] recovery strength,[8] and frequency of arrhythmias,[9] all have been observed as effects of aging.

The case we have presented may have been a demonstration of this so-called "devolution" process or, as Dock would suggest, "presbycardia."

Summary

In the case presented, symptoms and signs of cardiac insufficiency were manifest over a period of years and decompensation occurred twice. The last time it was fatal. Yet the heart was normal or anatomically unchanged at postmortem examination. This case may be one example of failure of the myocardium per se. The relation of muscle inadequacy to heart failure is discussed. It is postu-

lated that aging of the muscle fiber may have been intimately related to failure in this case.

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NEISSERIA FLAVA ENDOCARDITIS: WITH REPORT OF A CASE*

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ENDOCARDITIS due to *Neisseria flava* is apparently very rare, for we were able to find only three cases reported in the literature. The pigmented *Neisseria* are considered to be nonpathogenic inhabitants of the mouth and upper respiratory tract of man, and invade the tissues of the body on extremely rare occasions. Cases have been reported, however, of meningitis,[1, 2, 3, 4] of purulent cervicitis,[5a] of urethritis,[5a] and of inflammatory hydrocele,[5b] in which these organisms were found to be the causative agent. It appears pertinent, therefore, to present the following case of *Neisseria flava* endocarditis.

CASE REPORT

A Mexican girl, aged 14 years, was admitted to the gynecologic service of Hermann Hospital on February 26, 1947, complaining of fever, lower abdominal pain, vomiting, and generalized muscular aching of two days' duration, and severe headache of several hours' duration.

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She was well until five months prior to admission, when she developed a profuse vaginal discharge a few days following sexual intercourse. The discharge persisted without other manifestations until two weeks before admission, when she had a mild coryza and pharyngitis for three or four days; the other symptoms appeared two days prior to entering the hospital.

She was a well developed and nourished Mexican girl who appeared acutely ill. The oral temperature was 104.2° F.; the cardiac rate was 140 beats per minute, and the respirations were 26 per minute. A blowing systolic murmur of short duration was present over the entire precordium but was of the greatest intensity over the aortic area. The arterial pressures were 112 mm. of mercury systolic and 56 mm. diastolic. The abdomen was tender throughout, but the tenderness was greater in the lower quadrants. Muscular rigidity, however, was absent. A profuse yellowish-white, mucopurulent vaginal discharge was present without other demonstrable abnormalities in the pelvic organs. Widespread muscular tenderness was found without joint involvement. A catheterized urine specimen was not abnormal, and the hemoglobin and erythrocyte count were within normal limits. The leukocytes numbered 8,200 per cm. with a normal differential count; the erythrocyte sedimentation rate was prolonged.

Pelvic inflammatory disease was thought to be the cause of her illness, and 40,000 units of penicillin were administered intramuscularly every three hours for three days until 680,000 units had been given. At this time she was not improved; penicillin was discontinued, and she was transferred to the medical service. The oral temperature had varied from 100.4° to 105.8° F., and during the next 11 days it fluctuated between 99.0° and 103.6° F. Blood cultures obtained on the second and seventh hospital days showed no growth in dextrose brain, heart infusion broth. A gram-negative diplococcus was grown, however, from a blood culture obtained on the eighth hospital day and also on the fourteenth day. Transient diplopia and substernal distress appeared during the fourteenth hospital day. Two small splinter hemorrhages were noted under the fingernails, and the liver became palpable 2 cm. below the costal margin in the midclavicular line. The generalized abdominal and muscular tenderness persisted. A diagnosis of *Neisserian* endocarditis was made, and penicillin was administered intramuscularly in doses of 50,000 units every two hours, and oral sulfadiazine therapy was begun in doses of one-half gram every three hours. The following day a retinal hemorrhage was noted in the left eye. The body temperature declined during the next four days to normal, where it remained except for an occasional elevation to 99.4° F. for the next three weeks. Sulfadiazine therapy was discontinued after two weeks because of renal irritation, and penicillin was discontinued a week later after 13,400,000 units had been administered. The patient was free of symptoms, the cardiac murmur had diminished in intensity and was not audible at times, but the erythrocyte sedimentation rate was still prolonged. Three blood cultures had shown no growth. Pain reappeared in the left knee and thigh, and petechiae were noted under two fingernails on the ninth day without therapy. Intramuscular penicillin therapy was reinstated in doses of 100,000 units every two hours and was continued for 49 days. Her symptoms subsided within 48 hours and did not recur. The temperature rose occasionally to 99.4° F., and the sedimentation rate was slightly prolonged. The last positive blood culture was obtained on the tenth day after reinstitution of penicillin therapy and seven subsequent blood cultures showed no growth. She received 58,500,000 units of penicillin during the last course, and a total dosage of 72,580,000 units, and was discharged after 98 days in the hospital. The cardiac murmur had subsided, but the leukocyte count remained elevated, and the sedimentation rate was 22 mm. per hour when observed one month after discharge.

Repeated examinations of the urine failed to reveal any abnormality except during the sulfonamide crystalluria. Eosinophilia varied from zero to 21 per cent of the

leukocytes, and their presence is of unknown significance. Examinations of the spinal fluid and stools revealed no abnormality. Serologic examination by the Kolmer method was reported as 2 plus on admission, three weeks later as 4 plus, and two weeks later as negative. Quantitative Kolmer at the end of one month was 222111 and two weeks later, 000000. Blood agglutinin titrations were negative for the usual organisms. Smears obtained from the vagina and uterine cervix were negative, and cultures of material from the same sources made on chocolate agar media and incubated under 5 per cent carbon dioxide showed no growth.

To obtain growth of the cultures from the blood stream it was necessary to inoculate a 10 per cent ascitic fluid, brain-heart infusion broth containing penicillinase and para-aminobenzoic acid, and to incubate under 5 per cent carbon dioxide. Subcultures inoculated on blood agar plates and incubated under 5 per cent carbon dioxide showed small colonies with a pale yellow pigment. Smears made from these colonies, and stained by the Gram method, revealed a gram-negative diplococcus which appeared larger and more pleomorphic than *Neisseria gonorrheae* or *N. intracellularis*. These colonies gave a positive oxidase reaction, and the organism failed to ferment glucose, maltose, sucrose, levulose, and mannitol. Penicillin sensitivity tests carried out on representative cultures of the organism showed that 0.06 unit of penicillin per ml. inhibited growth. The organism was not pathogenic for mice when inoculated intraperitoneally and intracerebrally. Complement was completely fixed by the patient's serum in dilutions of 1 : 20 in the presence of an antigen prepared from the organism, but failed to fix complement in the presence of a gonococcal antigen. The antigens were prepared according to the method of Torrey.[8] There was no agglutination of a formalized suspension of heat-killed organisms by polyvalent antimeningococcal serum. The patient's serum agglutinated the organism in dilution of 1 : 80.

The patient was reëxamined three months after discharge, at which time the only abnormality noted was a faint systolic murmur at the apex of the heart. One blood culture gave no growth. One month later she suddenly developed a fever and pains in the lower left quadrant of the abdomen and down the anterior surface of both thighs. The systolic murmur was unaltered, and muscular and superficial tenderness was present across the lower fourth of the abdomen and over the anterior aspect of both thighs to the knees. The rectal temperature varied from 100° to 99° F. The leukocyte count was 17,000 on admission but promptly returned to normal. Three blood cultures showed no growth. Her symptoms subsided after a few days, and she was discharged on the nineteenth hospital day.

Discussion

The first case of endocarditis attributed to the pigmented *Neisseria* which we were able to find in the literature was reported in 1914 by Kämmerer and Wegner.[9] It occurred following tonsillectomy, and the organisms which were isolated from the blood stream and from the valvular lesions resembled *N. perflava* (flava I), but its fermentative powers were tested only in dextrose, maltose and levulose. A fatal case of endocarditis which developed following tooth extraction was reported in 1939 by Connaughton and Rountree.[10] The organisms grown from the blood stream and from the valvular lesions were identified as *N. flava*. They fermented dextrose and maltose, but failed to ferment sucrose, levulose and mannitol, and thereby would be classified as *N. subflava* (flava III, see table 1). The third case was one of endocarditis cured by sulfamerazine and was reported by Major and Johnson.[11] The organisms in this case resembled *N. perflava* (flava I), except for the fact that it was gram-positive and became gram-negative only after cultivation on artificial media for two months.

We are not certain whether the organism isolated from our patient is an aberrant strain of gonococcus or belongs to the pigmented group of *Neisseria*. The fact that enriched media and carbon dioxide were required for growth indicates that it belongs to the fastidious pathogenic *Neisseria* or that it is an unusual strain of the pigmented *Neisseria*. The morphology, pigment formation and sugar fermentations, on the other hand, suggest that it belongs to the pigmented

TABLE I

Fermentation Reactions of the Gram-Negative Diplococci

Pigmented Species	Dextrose	Maltose	Sucrose	Levulose	Mannitol
N. perflava (flava I)	+	+	+	+	+
N. flava (flava II)	+	+	−	+	−
N. subflava (flava III)	+	+	−	−	−
N. flavescens	−	−	−	−	−

Reproduced from Textbook of Bacteriology by Edwin O. Jordan and William Burrows, Thirteenth Edition, Revised, 1942, W. B. Saunders Company, Philadelphia and London, p. 333.

species. It is possible that chemotherapy altered the cultural characteristics of the organism.[12, 13] The organisms grown from the blood stream following the first course of penicillin therapy failed to ferment any of the sugars. On the other hand, those obtained from the blood stream following the combined penicillin and sulfadiazine therapy fermented all the sugars. The cultures of the organisms isolated originally were rechecked after several transfers on artificial media, and they fermented all of the sugars. In addition, it was found that these organisms would now grow without carbon dioxide. Carpenter [5a] surmised that the gonococcus may acquire additional enzyme systems when subjected to prolonged unusual environmental factors and thereby alter its biochemical activity. Wilson and Smith [14] concluded from their studies that colonial appearance, pigment formation, and fermentation reactions should not be used to classify the gram-negative cocci of the nasopharynx (exclusion of meningococcus) because these criteria were subject to alteration. Variations in the fermentation reaction and antigenic composition of the meningococcus are known.[3, 15]

The mode of entry of the organisms into the blood stream in our case may be open to question. It appears most likely that they entered from the vaginal and uterine cervical infection. She had manifestations, however, of acute coryza and pharyngitis approximately two weeks prior to the onset of the acute symptoms. In one of the reported cases, the organisms apparently entered the blood stream from the tonsillar fossae, in another from a tooth socket, while the source of the organisms in the third case was not specified. The fact that growth was not obtained in our case from the vaginal secretions does not exclude this as the infecting focus. Carpenter [5a] observed three patients with manifestations similar to gonorrhea, in two of which he isolated *Neisseria flava* II from the uterine cervix and from the urethra in the other. He refers to the isolation of a "diplococcus pharyngeus flavus III" from the uterine cervix of a prostitute by Coutts and Barthet,[6] and to the recovery of a pigmented *Neisseria* from the semen in two cases by Lankford.[5b] Such reports add credence to the likelihood that our patient had vaginitis and cervicitis due to the pigmented *Neisseria*.

It has been suggested by Reimann and Kouchy [4] that certain bacterial strains

ordinarily harbored in certain orifices of the body may produce disease if resistance of the host is reduced. Benson, Brennwasser and D'Andrea [1] concluded that, although the flava group had little pathogenicity in humans, they were able to produce disease in susceptible persons.

Summary

A case of endocarditis due to a species of pigmented *Neisseria* is reported. Only three such cases were found in the literature. The classification, the identification of the pigmented *Neisseria*, the difficulty of bacteriologic diagnosis, and the mode of entry into the blood stream are discussed.

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EDITORIAL

THE FOURTH GENERAL ASSEMBLY OF THE WORLD MEDICAL ASSOCIATION, OCTOBER 16 TO 20, 1950; REPORT OF THE OBSERVER FROM THE AMERICAN COLLEGE OF PHYSICIANS

THE World Medical Association, organized in 1946, has completed its fourth annual General Assembly, held this year in New York City. It is made up of representatives of the national medical associations of a large proportion of the nations of the world, not including those under the direct influence of the Soviet Union.* Because it is a non-political, non-governmental and independent agency, it is able to accomplish by private means many things which purely governmental agencies cannot do. Coöperation with such organizations is, however, part of its policy. The objectives of the Association, as stated in Article 3 of the Constitution, are as follows:

(1) To promote closer ties among the national medical organizations and among the doctors of the world by personal contact and all other means available.

(2) To maintain the honor and protect the interests of the medical profession.

(3) To study and report on the professional problems which confront the medical profession in the different countries.

(4) To organize an exchange of information on matters of interest to the medical profession.

(5) To establish relations with, and to present the views of the medical profession to, the World Health Organization, U.N.E.S.C.O., and other appropriate bodies.

(6) To assist all peoples of the world to attain the highest possible level of health.

(7) To promote world peace.

The General Assembly, which convenes annually, is made up of delegates from the Member-Associations, each of which sends two. The Assembly elects a Council which meets at least twice a year and is the Executive Committee of the Association. The Council consists of ten members, plus the President, President-elect and Treasurer ex-officio. A secretariat and various officials are appointed by the General Assembly.

At the present time Dr. T. C. Routley of Canada, one of the most active of those involved in organizing the Association, is Chairman of Council, Dr. Otto Leuch of Switzerland is Treasurer and Dr. Louis H. Bauer is Secretary-General. Dr. Dag-Knutson of Sweden is Vice-Chairman of Council and also is President-elect. The next meeting of the General Assembly will be held in Sweden and it appears to be the custom to elect the President from among the medical leaders of the country in which the meeting is to be

* The National Associations of Poland and Hungary were members but have been dropped because of non-payment of dues and failure to answer any correspondence.

held. Dr. E. L. Henderson is President this year and Dr. Hill, of England, presided over last year's Assembly which was held in London.

Perhaps the most important officials in the whole organization are the Assistant Secretaries, each of whom is responsible for a large area of the world. They are as follows:

Dr. J. A. Bustamante of Cuba for Latin America.
Dr. Paul Cibrie of France for Europe.
Dr. John Hunter of Australia for Australasia.
Dr. S. C. Sen of India for Asia.

Having heard these men in action at the meeting of the Assembly this Observer can bear testimony to their earnestness of purpose, ability in discussion and evident high ideals of service to the people of the areas which they represent.

It is of interest that the present General Assembly consists of delegates from 39 countries. These range in size from great nations such as India, Great Britain and the United States to Iceland, San Salvador and Luxembourg.

The main business of the fourth Assembly was the consideration of the reports of the Council on its activities since the last Assembly, of the Assistant Secretaries on medical problems arising in their various areas, and of committees which have been created for the study of specific subjects, the most important of which appeared to be Social Security and medical education and practice throughout the world. In addition there were, of course, some matters of necessary routine such as financial reports and the election of officers and members of the Council. Reports also were received from official Observers to other bodies including the World Health Organization, U.N.E.S.C.O., International Red Cross and others. Dr. Brock Chisholm, Director of W. H. O., addressed the Assembly and outlined the activities of his organization. No attempt will be made in this report to present the details of the proceedings which will be published in full in the Bulletin of the Association of which Morris Fishbein is Editor.

One afternoon of the Assembly was given over to a Scientific Session, financed by a grant from the U. S. Public Health Service, at which presentations were made by Doctors Alfred Blalock, Louis K. Diamond, Hans Selye and Albert F. R. Andresen. There was also an excellent program of entertainment for the ladies who accompanied delegates and Observers. This included a sight-seeing trip about New York, a tour of the Metropolitan Museum, luncheons, teas and a trip to the United Nations at Lake Success. An interesting and valuable feature of the conference was the Social program which, besides the special entertainment provided for the ladies, included a luncheon and a dinner every day, each tendered by one of the large pharmaceutical firms, and a final dinner given by the A. M. A. to which all were invited. A trip was made to West Point where a special luncheon with an excellent address by the Superintendent General Moore was followed by a tour of the grounds, an organ recital, a pathological exhibit by the Medical Department and finally a full-dress review by the cadet corps. In the opinion of this Observer, even if the deliberations of the Assembly itself had yielded

nothing of significance, which was by no means the case, the social program with the opportunity for informal contact and discussion between the leaders of medicine from all parts of the world would have amply justified the conference.

Of the proceedings of the Assembly the most important were, in the opinion of this Observer, the discussion of the Social Security schemes and resulting conditions of medical practice as found in various countries and the studies of medical education throughout the world. Also of interest were a few topics on which there was a sharp difference of opinion among the delegates, with a certain amount of spirited debate. The problem of action on the applications for membership from the Medical Associations of Japan and Western Germany is a case in point. The motion to empower the Council to accept these applications after further study and correspondence with member-associations, so that they might attend the 1951 session as full members, was vigorously opposed by Israel whose delegates contended that despite their formal disavowal, the Physicians of Germany could not be cleared of the terrible crimes committed under the Nazi regime and, therefore, should not be admitted at this time. Though there was evident sympathy with this attitude, the delegates from France, the Netherlands and Belgium spoke in favor of the motion which was passed with but three dissenting votes. Another controversial issue was the statement in the Council report condemning Euthanasia "in any form." Many delegates expressed a moderate and humanitarian view on this subject which "horrified" the delegate from Eire, while the able and distinguished Dr. Sen of India maintained in a masterly address that the governments and physicians of the various countries of the world should be allowed to decide this question according to their own lights, and that no declaration by the W. M. A. was appropriate. However, the report of the Council, condemning Euthanasia, eventually was adopted by a rather narrow margin.

The report of the Committee on Medical Education evolved considerable discussion. This report was admittedly incomplete because so many of the member-associations had not yet returned the questionnaire which had been circulated by the committee. Furthermore, the report pointed out that the World Health Organization has an expert committee on this subject, a duplication of whose work should be avoided. Nevertheless an interesting discussion ensued, based partly on supplementary reports by the British and American Medical Associations. The status of the general practitioner was singled out as a particularly important topic. Many countries had reported that they had too many specialists. The need of some type of "Marshall Plan," sponsored by all nations, to help the development of medical education in certain areas was stressed. In this connection Dr. Sen of India made a strong personal appeal for help addressed principally to the physicians of Canada and the United States. He called attention to the fact that in India with its population of 350,000,000 there are barely 50,000 trained physicians. He reported further that there are five or six times that many irregular practitioners (mostly adherents of two traditional cults) but that if they

were taken away the majority of the people would have nobody at all to whom to turn. The need is for at least 300,000 trained physicians, and the medical schools of the country turn out but 2,000 new doctors a year. Colleges, buildings, equipment and teachers are needed. He was also ready to assure the A. M. A. and the C. M. A. that medical and graduate students trained in the United States or Canada would with almost no exceptions, return to India for their life work. In contrast to the situation in India, both France and Ireland reported a surplus of physicians and both indicated that a number of their doctors are ready to emigrate to other lands, wherever they can be assured of favorable conditions for living and practicing their profession. The British delegates described the difficulties under which the general practitioner labors in the United Kingdom and a delegate from Sweden stressed the shortage of doctors in rural areas in his country and the need for their redistribution. He also mentioned the difficulty with which foreign doctors are faced in attempting to practice among Swedish people, a difficulty which, he believes, will hamper the progress of 100 Austrian physicians who are being imported by the government against the expressed wishes of the Medical Association. At the end of the discussion it was advocated that the World Medical Association carry out a study of shortages and surpluses of physicians throughout the world.

The report on Social Security Schemes was also of great interest. A preliminary study was published by the Association in the Spring of 1950, in which the schemes for Social Security now in operation in various countries were described in some detail. Dr. Knutson (delegate from Sweden and President-elect) stated that in countries where they are highly developed such schemes were usually planned and sponsored by politicians, and the doctors were not included. The attitude of the politicians has been that the doctors are not able to approach these questions with an unprejudiced point of view. On the other hand it has been thought by some that the politicians are not quite disinterested. The psychology of the situation has usually been wrongly interpreted—with the help of a powerful and ordinarily badly informed press. The creators of these schemes promise more than the doctors can possibly deliver, costs become extremely heavy, public opinion usually sides with the politicians and the doctors face a dilemma. With excessive costs, standards of service tend to be lowered. Dr. Knutson suggests that further study with a view to the offer of help to national associations faced with these problems would be in order.

The abuses which occur under many of the current social security plans, perpetrated by patients and by physicians too, were pointed out by Dr. Cibrie of France. Dr. Gloria of Belgium, emphasizing that nationalization of medicine is a fact in some countries, pointed out that the intrusion of politics into the situation, and a lack of appreciation of human psychology are the most damaging factors in such a situation and that the catastrophic increase in expenditure over previous costs is the outstanding fact. These excessive costs depend on (1) the assumption of additional obligations under the scheme, (2) the necessity of using modern complicated technics, (3) the

increasing intricacy of administrative machinery and (4) an increase in the volume of medical services, caused by the increased demands of the patients (who do not have to pay for what they get).

Considerable discussion of the situation in Great Britain ensued, and the fact that the present system was made necessary by the impoverished state of the country at the end of the war was stressed. Dr. Sen of India advocated a differentiation between Social Security and Medical Security and cited the prevention of hunger, unemployment, ignorance, lack of shelter and of clothing as essentials to the attainment of Social Security. With these objectives unrealized, he believed that the attainment of Medical Security must be an impossibility. Resolutions embodying a logical interpretation of the facts regarding social security schemes and the planning of further study and attempts to aid in situations where aid is possible were adopted.

A number of other matters of considerable interest were taken up by the Assembly. Among these were reports on the nomenclature of disease and on an international pharmacopeia. The report of Dr. Fishbein on the Bulletin brought forth the fact that this publication is now self-supporting and may be expected in the near future to contribute substantially to the support of the Association. The financial report of Dr. Otto Leuch, the Treasurer, and that of the United States Committee were also of interest. The fact was brought out that at present about 90 per cent of the financial support of the W. M. A. is from the United States. In this connection Dr. Routley reminded the Assembly that three years ago the U. S. delegation had virtually promised to raise $50,000 a year for three years and already in each of the first two years they had materially exceeded that sum.

The United States Committee is the name given to the group of American physicians who have individually contributed to the support of the World Medical Association. It is incorporated and runs on a separate budget. This support has been essential to the success of the Association. All members of this Committee are entitled to attend the Assembly as Observers and a large number, approximately 156, of physicians availed themselves of this privilege.

A more detailed account of the actions of the Assembly, such as will be available in the published minutes, cannot be included in a report of this nature. This statement attempts merely to reflect the "feel" of the meeting, to mention its more significant activities, and to assess the value of the W. M. A. as an organization both to the people and to the physicians of the world. In the opinion of this Observer the World Medical Association, representing as it does the medical profession of most of the world, collaborating with W. H. O., U.N.E.S.C.O. and other agencies, can be a real factor in the attainment of its main objectives, world wide improvement in medical education and practice, world wide improvement in the health of the people, and world peace. It deserves the support, individually or collectively, of every American physician.

ALEX. M. BURGESS, M.D.

REVIEWS

Pathology of Internal Diseases. 5th Ed. By WILLIAM BOYD, M.D., F.R.C.P., F.R.C.S., LL.D., D.Sc., F.R.S., Professor of Pathology and Bacteriology in the University of Toronto. 866 pages with 391 illustrations and 11 colored plates; 15 × 23 cm. 1950. Lea and Febiger, Philadelphia. Price, $11.00.

This is a welcome new edition. Many completely new sections have been added since the last edition in 1944. These are devoted to the L. E. cell, diffuse collagen diseases, temporal arteritis, choline deficiency hypertension, Löffler's pneumonia, anthracosilicosis, beryllium and bauxite pneumonias, pulmonary moniliasis, idiopathic pulmonary hemosiderosis, the renal lesions in diabetes, Ellis' classification of glomerulonephritis, the relation of the kidney to hypertension, renal anoxia, folic acid deficiency anemia, the anemia of chronic infections, congenital hemolytic disease, primary splenic neutropenia, myeloid metaplasia, histiocytic medullary reticulosis, Kernohan's new classification of the gliomas, diseases of bones and joints, and cortisone in rheumatoid arthritis. From which it can be seen that this text has been greatly augmented, although it exceeds its predecessor by only nine pages.

The content of these new sections is sound, though a number of them are not above criticism. For example the section on primary splenic neutropenia is good as far as it goes. It is unaccompanied, however, by any account of the equally well recognized hypersplenic syndrome of pancytopenia. Moreover, no suggestion that an hormonal mechanism may be involved in hypersplenic syndromes is made, for which there is much evidence. Then in the section devoted to splenic function it is stated that splenectomy is followed by erythropenia. The well known effect of splenectomy on the platelets and other formed elements of the blood, however, is not mentioned. Altogether more should be said of the spleen itself and of hypersplenism.

Again, while it is a great delight to see an authority like Dr. Boyd give publicity to Ellis' classification of the glomerulonephritides—a classification which has seemed for many years to the reviewer to be the best and least confusing—yet justice has not been done to the concept of "chronic nephritis" as Ellis propounds it.

The sections on the pathology of coronary occlusion, the tetralogy of Fallot, bronchiectasis, the apical distribution of pulmonary tuberculosis, emphysema, hepatitis and cirrhosis, Cushing's syndrome, poliomyelitis, and multiple myeloma have been rewritten.

The author's practice of including a section wherever possible on the relation of symptoms to lesions is a helpful and commendable one, but his attempts in Chapter I to correlate electrocardiographic changes with lesions is worse than useless. They would probably be better omitted than included in their present form; for example we are told that the particular change indicating myocardial involvement in coronary insufficiency is prolongation of the QRS complex. Nor can one let the simple and erroneous statement that the hypertension of hyperthyroidism "is due for the most part to the rapid heart-rate" pass unchallenged.

A full bibliography is appended at the end of each chapter, but the author persists in his method of classifying references by subject, which frequently makes an individual reference unnecessarily hard to track down; a simple alphabetical listing of authors would be a great improvement.

These and other minor deficiencies will not prevent this book, however, from retaining its position as a deservedly popular standard work of reference.

H. J. L. M.

Pathologie des Kohlehydratstoffwechsels. By PROF. DR. E. FRANK. 342 pages; 22.5 × 15.5 cm. 1949. Benno Schwabe & Co. Verlag, Basel; imported by Grune & Stratton, Inc., New York. Price: Fr. 24.

The author is the Director of the II. medizinischen Klinik of the University of Istanbul. His medical background is German, but his outlook on medical science is international in scope. In this volume of 342 pages he deals with the pathologic disturbances of carbohydrate metabolism. The development of the subject is chiefly from the physiologic aspect. The biochemical problems are touched only lightly and the clinical aspects hardly at all.

The book begins with a brief but very interesting historic summary of the classical experiments by which our present knowledge of the control of sugar metabolism was attained. The contributions of Claude Bernard, Minkowski, Banting, Houssay, Young and Long are signaled out for particular attention. This section ends with a discussion of alloxan diabetes. The author has the gift of describing crucial experiments in sufficient detail to stimulate the critical faculties of the reader. The student and the internist will profit from this masterly condensation of the major advances in our knowledge.

Thereafter, the treatment of the subject is to some extent topical. Sections are devoted to pituitary forms of diabetes; to the chemical nature, secretion and ultimate source of insulin; to theories of diabetes mellitus; to the pathology of the islets in diabetes mellitus and in primary diffuse pancreatic disease; to acidosis and coma; to hyperinsulinism; to glycogen storage disease; to the problem of the renal threshold for sugar; to the rarer forms of mellituria. A short terminal section of addenda brings in the most recent publications.

The author has lived through the era of great advances he describes. A student under Minkowski, he has worked and studied in the field of carbohydrate metabolism through a long professional life. The book shows that his interest in this field is still alive and vital and keeps him abreast of the latest developments.

The physician with moderate facility in reading the German language will find study of this book an excellent method of bringing into an ordered pattern his knowledge of the disorders of carbohydrate metabolism.

M. C. P.

The Antihistamines. 1st Ed. By SAMUEL M. FEINBERG, M.D., Associate Professor of Medicine; SAUL MALKEIL, M.D., Assistant Professor of Medicine; and ALAN R. FEINBERG, M.D., Clinical Assistant in Medicine; Northwestern University Medical School. 291 pages; 12.5 × 18.5 cm. The Year Book Publishers, Inc., Chicago 11, Illinois. 1950. Price, $4.00.

This volume reflects the senior author's ability to write clearly, to organize his material well, and to cover a subject adequately.

The volume is divided into two main sections, the first dealing with experimental studies and the second with clinical considerations. The first section discusses histamine, particularly its rôle in specific sensitivity, both in animals and in man; and the chemistry of the antihistamines, their pharmacology, their rôle in experimental hypersensitivities, and methods of performing bioassays in man.

The second section discusses rather thoroughly the rôle of the antihistamines in clinical manifestations of allergy, their administration and dosage, and their toxic effects.

That portion of the book having to do with the selection of a proper antihistamine in a given condition is excellent. The authors also discuss combinations of these drugs with other agents and, rightfully, in the opinion of the reviewer, condemn the practice. The authors' conclusion, that the treatment of hay fever solely with the

antihistamine drugs is dangerous because of their failure to prevent asthma in that large percentage of cases exhibiting this syndrome, is most timely. Further, the enthusiasm of the authors for these drugs is gratifyingly restrained. The remarks of the authors upon the use of the antihistamines in the "common cold" are also most timely. They condemn them as being relatively useless and, possibly, even dangerous, particularly because of the unwholesome practice of "over the counter" sales.

The reviewer is of the opinion that the form of Histadyl available for intramuscular injection should have been mentioned because it has been found to be most useful in intractable urticaria.

The book contains an excellent and complete bibliography. For allergists, and as a source reference book, the volume is to be commended. For ordinary clinical use by the general man, it would seem that it is too complete.

H. B.

Principles and Practice of Therapeutic Exercises. By HANS KRAUS, M.D. 309 pages; 16 × 23.5 cm. Charles C. Thomas, Springfield, Illinois. 1949. Price, $6.50.

The book as a whole is excellent as a guide in the use of exercise as a therapy, in that it explains well the physiology of muscular action and the stresses and strains put upon muscles normally and abnormally with the pathological changes thereby produced.

The summary on the book-cover aptly describes what the book offers: "How to prepare and carry out a therapeutic exercise program on a basis of rational planning and not chance means," and "How to direct the proper type and amount of exercise to the muscles requiring treatment."

The book is divided into three parts, the first two of which deal with the individual muscle and the third, with general exercise for its effect upon the body as a whole. Part I: Chapter 1 establishes certain physiological facts about muscles and explains them, then gives the changes and the reasons in certain pathological situations. Chapter 2 presents methods of evaluating the features occurring in muscles in action. Chapter 3 deals with technics which can bring about the effects desired. Chapter 4 gives sound explanations of pain and spasm and gives good advice as to their handling. Chapters 5 and 6 emphasize the part of the physician in prescribing specific directions (prescription writing) and some good advice regarding variations and limitations in activities and habits, etc.

Part II covers a large variety of specific pathological conditions, which may be helped by proper use of exercise. This is a most valuable section and could be referred to frequently by all in the field.

Part III treats only briefly with the large field of general exercise.

There is an extensive bibliography preceding the index.

A. F. V.

Stillbirths, Their Epidemiology and Social Significance. By IAN SUTHERLAND; with a foreword by John A. Ryle. 93 pages; 21.5 × 14 cm. Oxford University Press, New York. 1950. Price, $1.50.

Detailed statistical analyses of stillbirths correlated with biological and social factors are applied to this study of the total of 53,000 stillbirths, neonatal deaths, and deaths under one year of age occurring in England and Wales annually.

This excellent monograph should be of interest to biostatisticians, obstetricians, health officers, nutritionists and social scientists, to which groups it is highly recommended.

J. E. S.

Aetios of Amida: the Gynaecology and Obstetrics of the 6th Century A.D.; translated from the Latin Edition of Cornarius, 1542, and fully annotated. By JAMES V. RICCI, M.D. 215 pages; 24 × 15.5 cm. The Blakiston Company, Philadelphia. 1950. Price, $7.00.

A great text on gynecology and obstetrics written 14 centuries ago is presented in modern form, having been translated and annotated by the eminent gynecologist-historian, Dr. Ricci. The contents represent the sixteenth or last book of an encyclopedia of medicine by AETIOS of AMIDA, who was a renowned Byzantine physician and medical author. In this fascinating book one finds detailed descriptions of disease, therapeutic principles and substances, and operative technics in vogue in the sixth century A.D. Obstetricians, gynecologists and medical historians will find pleasant and instructive reading in this volume.

J. E. S.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Differential Diagnosis of Internal Diseases: Clinical Analysis and Synthesis of Symptoms and Signs. By JULIUS BAUER, M.D., F.A.C.P., Clinical Professor of Medicine, College of Medical Evangelists, Los Angeles, etc. 866 pages; 23.5 × 16 cm. 1950. Grune & Stratton, Inc., New York. Price, $12.00.

Fortschritte auf dem Gebiet der Kreislauferkrankungen. 15. Fortbildungslehrgang in Bad-Nauheim vom 14.–16. Oktober 1949. HERAUSGEGEBEN VON VEREINIGUNG DER BAD-NAUHEIMER ÄRZTE. 91 pages; 24.5 × 17 cm. (paper-bound). 1950. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, DM 9.–

Life Stress and Bodily Disease: Proceedings of the Association for Research in Nervous and Mental Diseases, December 2 and 3, 1949, New York, N. H.—Volume XXIX. Editorial Board: HAROLD G. WOLFF, M.D., STEWART G. WOLF, JR., M.D., and CLARENCE C. HARE, M.D. 1135 pages; 23.5 × 16 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $15.00.

Manson's Tropical Diseases: A Manual of the Diseases of Warm Climates. 13th Ed. Edited by SIR PHILIP H. MANSON-BAHR, C.M.G., D.S.O., M.A., M.D., D.T.M. and H. Cantab., F.R.C.P., London, Past President of the Royal Society of Tropical Medicine and Hygiene, London, and the Medical Society of London, etc. 1136 pages; 22.5 × 14 cm. 1950. The Williams & Wilkins Company (A William Wood Book), Baltimore, Maryland. Price, $9.00.

Medical Entomology, with Special Reference to the Health and Well-being of Man and Animals. 4th Ed. By WILLIAM B. HERMS, Sc.D., Late Professor of Parasitology, Emeritus, University of California, etc. 643 pages; 24.5 × 15.5 cm. 1950. The Macmillan Company, New York. Price, $9.00.

Der Muskelstoffwechsel des Herzens: Seine Physiologie, Pathologie und Klinik. By DR. MED. HABIL. HEINRICH SCHUMANN. 150 pages; 24.5 × 16.5 cm. (paper-bound). 1950. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, DM 14.50.

Parkinson's Disease: Advice and Aid for Sufferers from Parkinson's Disease and Other Physical Disabilities. By WALTER BUCHLER. 79 pages; 19 × 12.5 cm. 1950. Walter Buchler, London. Price, $2.00.

The Physician Examines the Bible. By C. RAIMER SMITH, B.S., M.D., D.N.B. 394 pages; 21.5 × 14 cm. 1950. Philosophical Library, New York. Price, $4.25.

The Results of Radium and X-Ray Therapy in Malignant Disease: Being the Third Statistical Report from the Radium Institute, The Christie Hospital and Holt Radium Institute, Manchester, Years 1940 to 1944 inclusive assessed at 5 years and 1934 to 1938 assessed at 10 years. Compiled by RALSTON PATERSON, MARGARET TOD and MARION RUSSELL. 167 pages; 25 × 15.5 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $2.50.

A Syllabus of Laboratory Examinations in Clinical Diagnosis: Critical Evaluation of Laboratory Procedures in the Study of the Patient. Edited by THOMAS HALE HAM, B.S., M.D., Assistant Professor of Medicine, Harvard Medical School, etc. 496 pages; 27.5 × 21 cm. (paper-bound). 1950. Harvard University Press, Cambridge. Price, $5.00.

COLLEGE NEWS NOTES

The American College of Physicians Announces Research Fellowship Awards for 1951–52

Since 1934 the American College of Physicians has had an active Research Fellowship program, designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. The annual stipend is $3,000.00, single; $3,500.00, married.

The Alfred Stengel Research Fellowship, established in 1947, was founded in part under the terms of a grant made by the late Dr. James D. Bruce in honor of a former President of the College, Dr. Alfred Stengel (now deceased), who was responsible in a large measure for laying the foundations of the American College of Physicians as its members know it today. The Committee on Fellowships and Awards selects the Alfred Stengel Research Fellow from the Research Fellows nominated each year as the one who in their judgment offers greatest promise of attaining unusual distinction in investigation, teaching and as a clinician. The stipend for this Fellowship is $3,500.00, single; $4,000.00, married.

At a meeting of the Board of Regents on November 12, 1950, the following Research Fellowships were awarded for the period July 1, 1951—June 30, 1952:

Regular Research Fellowships:

John William Athens, M.D., Duluth, Minn.; a graduate of the Johns Hopkins University School of Medicine, 1948; to study the phenomenon of protein regeneration, under F. W. Barnes, Jr., M.D., of Johns Hopkins Hospital, Baltimore, Md.

Amoz Immanuel Chernoff, M.D., New Haven, Conn.; a graduate (cum laude) of Yale University School of Medicine, 1947; to do investigative work in the group of hemolytic anemias, both hereditary and acquired, under Carl V. Moore, M.D., F.A.C.P., in the Department of Internal Medicine, Barnes Hospital, St. Louis, Mo.

Sidney Harold Ingbar, M.D., Watertown, Mass.; a graduate of Harvard Medical School, 1947; to work in the field of metabolic physiology of infection and the rôle of the endocrine glands in the response of the organism to infection, under Maxwell Finland, M.D., F.A.C.P., Thorndike Memorial Laboratory, Boston City Hospital, Boston, Mass.

John Edmund Kiley, M.D., Delmar, N. Y.; a graduate of Harvard Medical School, 1945; to work in the field of medical aspects of renal disease, under A. V. Wolf, M.D., and William B. Deichmann, M.D., in the Department of Physiology of the Albany Medical College, Albany, N. Y.

James Edwin Wood, III, M.D., Charlottesville, Va.; a graduate of Harvard Medical School, 1949; to carry on plethysmographic studies of the circulation in the extremities, under Robert W. Wilkins, M.D., F.A.C.P., Evans Memorial, Massachusetts Memorial Hospitals, Boston, Mass.

The Alfred Stengel Research Fellowship:

John William Harris, M.D., Boston, Mass.; a graduate of Harvard Medical School, 1944; to work in the field of pathophysiology of the anemias, under William B. Castle, M.D., F.A.C.P., Thorndike Memorial Laboratory, Boston City Hospital, Boston, Mass.

Dr. Benjamin B. Wells Awarded First A. Blaine Brower Traveling Scholarship

The Board of Regents on November 12, 1950, awarded the first A. Blaine Brower Traveling Scholarship of the American College of Physicians to Dr. Benjamin B. Wells (Associate), Professor of Medicine at the University of Arkansas School of Medicine, Little Rock, Ark. Dr. Wells will spend several weeks during the early part of 1951 pursuing a program of inspection and study of the organization and administration of undergraduate teaching in internal medicine. The Committee on Fellowships and Awards of the College will arrange and organize a tour of several of our leading medical schools. Important changes have been made during recent years in the undergraduate teaching program for internal medicine. Full-time teachers must face these changes fully informed in the interest of their specialty, good medical teaching and the welfare of the American public. In this particular instance, the Committee has awarded this scholarship in the interest of medical teaching—encouragement for sound, well-organized teaching.

An endowment trust in the amount of $10,000 was established by Dr. A. Blaine Brower, F.A.C.P., a Regent of the College, with the provision that the income shall be used for a periodic or annual traveling fellowship. The donor's aim is to provide an opportunity for a worthy young physician, preferably an Associate of the College, to spend a month, more or less, as a visiting fellow at some institution, or institutions, for observation and postgraduate study. The Committee on Fellowships and Awards of the College can readily facilitate opportunities for this fellowship at outstanding institutions where a month's observation, contact and study will be an exceptional inspiration and a practical source of training.

For 1951 there were 46 candidates, all with exceptionally worthy proposed programs. Under the circumstances, selection of but one candidate for the scholarship naturally was most difficult. The plan opens up a whole new field of service, and the Board of Regents unanimously voted to allocate from the general Endowment Fund another $10,000, to extend in 1952 another such scholarship, both scholarships to be known as the "A. Blaine Brower Traveling Scholarships." The effectiveness of the scholarships will be carefully observed; other Fellows may wish later to contribute for similar projects.

Growing Popularity of A.C.P. Regional Meetings

Regional meetings of the state or multi-state variety have been conducted on a moderate scale for many years, but probably the greatest impetus to this activity of the College has developed during the current year. Not only have the number of regional meetings greatly increased, but the programs have improved in excellence, resulting in a marked increase in attendance and general interest. These regional meetings are held not only in communities or states where there is a large College membership, but also in states such as Mississippi, North Dakota, Montana, Wyoming, Puerto Rico, et al., where College membership necessarily is limited. Numbers alone are not necessarily significant but percentages and quality are. In no single instance have programs been weak, interest lacking or results disappointing.

Space in this section of the Annals of Internal Medicine does not permit the publication of the full programs and details concerning each and every meeting. It is, however, interesting to note attendance records for the following meetings:

Other regional meetings scheduled but not yet reported upon at the time of the preparation of this item include the Midwest Regional Meeting, Madison, Wis., November 18, 1950; North Carolina, at Chapel Hill, December 8, 1950; Kentucky, at Lexington, December 9, 1950; Midsouth, at Memphis, January 12–13, 1951; South-

Territory	Place of Meeting	Date	Registration
North Dakota	Minot	September 9, 1950	34
Montana-Wyoming	Billings	September 15–16, 1950	34
Western Pennsylvania	Pittsburgh	September 27, 1950	200
Oklahoma-Arkansas	Tulsa	September 30, 1950	91
Mississippi	Jackson	October 7, 1950	52
Northern California	San Francisco	October 13, 1950	109
Southern California	Los Angeles	October 14, 1950	191
Arizona	Tucson	October 14, 1950	62
North west	Portland, Ore.	October 27–28, 1950	110
New Jersey	Trenton	November 1, 1950	156
Puerto Rico	San Juan	November 5, 1950	Not yet reported
Utah	Salt Lake City	November 11, 1950	Not yet reported

eastern, at Charleston, January 26–27, 1951. Other regional meetings in course of organization include Colorado, at Denver, February 20, 1951; Nebraska, at Omaha, February, 1951; Virginia, at Roanoke, February, 1951; Eastern Pennsylvania, at Philadelphia, February 9, 1951; Delaware, at Wilmington, February 22, 1951; Kansas, at Wichita, March 16, 1951; Maryland and the District of Columbia, at Washington, February, 1951.

In New Jersey, it has been determined to hold the annual Regional Meeting regularly each year the first Wednesday of November.

Midsouth Regional Meeting—American College of Physicians

The Midsouth Regional Meeting of the American College of Physicians, representing the states of Louisiana, Texas, Tennessee, Alabama, Arkansas and Mississippi, will be held in Memphis, Tenn., January 12–13, 1951 under the general chairmanship of Dr. William C. Chaney, F.A.C.P., Memphis, Governor for Tennessee.

A very complete program has been planned, beginning with registration and luncheon on Friday, January 12, 1951. Included on the program for Friday afternoon are the following:

L. W. Diggs, M.D. (by invitation), Memphis, Tenn., "The New Nomenclature for Blood Cells."

A. C. Guyton, M.D. (by invitation), University, Miss., "Studies on Controlled Acute Cardiac Failure."

C. H. Burnett, M.D. (by invitation), Dallas, Tex., "Adrenal Pituitary Relationships in Renal Function."

Edgar Jones, M.D., F.A.C.P., Nashville, Tenn., "Comments on Pernicious Anemia."

Daniel E. Jenkins, M.D., (Associate), Houston, Tex., "Recent Advances in the Treatment of Tuberculosis."

Arthur Grollman, M.D., F.A.C.P., Dallas, Tex., "An Experimental Study of Methods for the Prolongation of Life in the Nephrectomized Dog and Its Application to the Human."

Willard O. Thompson, M.D., F.A.C.P., Chicago, Ill., "ACTH and Cortisone."

A reception and informal banquet will be held Friday evening for the Fellows, Associates and their wives. Dr. O. W. Hyman, Dean of the University of Tennessee College of Medicine, will act as toastmaster. The address will be delivered by Dr. William S. Middleton, F.A.C.P., President of the College. Other distinguished guests include Dr. George Morris Piersol, M.A.C.P., Secretary-General and Past President

of the College, Philadelphia; Dr. James E. Paullin, M.A.C.P., Past President of the College and Past President of the American Medical Association, Atlanta; Mr. E. R. Loveland, Executive Secretary of the College, Philadelphia and Colonel Jack Major.

The Saturday program, beginning at 9:00 a.m., will include the following:

CHARLES T. STONE, M.D., F.A.C.P., Galveston, Tex., "Portal Hypertension: Clinical and Therapeutic Considerations."

THOMAS FINDLEY, M.D., F.A.C.P., New Orleans, La., "The Kidney as an Endocrine Gland."

GEORGE R. HERRMANN, M.D., F.A.C.P., Galveston, Tex., "Clinical Aspects and Management of Atrial Flutter."

HAROLD S. JACOBS, M.D. (by invitation), New Orleans, La., "Angiocardiography in the Definitive Diagnosis of Cardiovascular Disease."

W. R. AKENHEAD, M.D. (by invitation), New Orleans, La., "The Dilemma of Multitudinous Leads in Clinical Electrocardiography."

BENJAMIN B. WELLS, M.D., (Associate), Little Rock, Ark., "Laboratory Procedures for Diagnosis and Control of Therapy in Rheumatoid Arthritis."

HENRY PACKER, M.D., F.A.C.P., Memphis, Tenn., "Problems and Their Management in Central Nervous System and Cardiovascular Syphilis."

Present plans call for the Midsouth Regional Meeting to be held in Louisiana in 1951 and in Texas in 1952. Further details and information on hotel reservations may be obtained from Dr. J. F. Hamilton, F.A.C.P., Chairman of Committee on Arrangements, 869 Madison Avenue, Memphis 3, Tenn.

VIRGINIA STATE SECTION OF THE AMERICAN COLLEGE OF PHYSICIANS ELECTS OFFICERS AND PLANS 1951 REGIONAL MEETING

The Virginia State Section of the American College of Physicians had a luncheon-business meeting at Roanoke, Va., Tuesday, October 10, 1950, during the meeting of the Medical Society of Virginia from October 8 to 11. C. D. Nofsinger, M.D., F.A.C.P., of Roanoke, was elected Chairman, and James F. Waddill, M.D., F.A.C.P., of Norfolk, was reëlected Secretary-Treasurer.

It was decided that the winter scientific meeting would be held in Roanoke, Va., in 1951, at some time during the latter part of February. General information concerning this meeting will be distributed to the Virginia members at a later date by the local Program Committee.

The business meeting was addressed by Douglas G. Chapman, Jr., M.D., F.A.C.P., of Richmond, Chairman of the Section for 1949–1950, by Charles M. Caravati, M.D., F.A.C.P., Richmond, College Governor for Virginia, and J. Morrison Hutcheson, M.D., F.A.C.P., Richmond, former member of the Board of Regents and former Vice President of the College.

A.C.P. POSTGRADUATE COURSES—SPRING, 1951

The following is the schedule of Postgraduate Courses approved by the Advisory Committee on Postgraduate Courses and the Board of Regents at a meeting on November 12, 1950. Certain of these courses are definite and their dates are established; others are tentative, subject to selection of dates.

MODERN TRENDS IN DIAGNOSIS AND TREATMENT OF HEART DISEASE: William G. Leaman, Jr., M.D., F.A.C.P., Director; Woman's Medical College of Pennsylvania and Other Philadelphia Institutions; Philadelphia, Pa.; January 22–27, 1951.

Any physician desiring to register for the above course (detailed outline follows) should do so immediately. This course will be one of the most outstanding courses in Cardiology ever offered by the College. Eminent teachers from various parts of the United States appear on the faculty. Probably no postgraduate course of this character has ever been given by a group of such eminent teachers and clinicians.

PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES: George C. Griffith, M.D., F.A.C.P., Director; University of Southern California School of Medicine, Los Angeles, Calif.; February 12–17, 1951.

RECENT PROGRESS IN INTERNAL MEDICINE: Howard P. Lewis, M.D., F.A.C.P., Director; University of Oregon Medical School, Portland, Ore.; March 19–23, 1951.

ELECTROCARDIOGRAPHY: Gordon B. Myers, M.D., F.A.C.P., Director; Wayne University College of Medicine, Detroit, Mich.; March 26–31, 1951.

INTERNAL MEDICINE: Garfield G. Duncan, M.D., F.A.C.P., Director; Pennsylvania Hospital, Philadelphia, Pa.; May 7–11, 1951.

ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION: Conger Williams, M.D., Director; Massachusetts General Hospital, Boston, Mass.; one week, date to be determined.

DYNAMIC THERAPEUTICS IN CHRONIC DISEASES: Howard A. Rusk, M.D., F.A.C.P., Director; New York University-Bellevue and Goldwater Hospitals, New York, N. Y.; one week, date to be determined.

DISEASES DUE TO IMMUNE MECHANISMS: Leo H. Criep, M.D., Director; University of Pittsburgh School of Medicine, Pittsburgh, Pa.; one week, date to be determined.

INTERNAL MEDICINE: Chester S. Keefer, M.D., F.A.C.P., Director; Boston University School of Medicine and Massachusetts Memorial Hospitals, Boston, Mass.; one week, date to be determined.

Fees: Registration Fees, A.C.P. Members, $30.00; Non-members, $60.00—except the Course in ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTREPRETATION, for which, due to a limited registration, fees will be $60.00 for Members; $120.00 for Non-members.

The Postgraduate Bulletin containing further details about faculty and content of these courses may be obtained on request to the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

COURSE NO. 9—MODERN TRENDS IN DIAGNOSIS AND TREATMENT OF HEART DISEASE

(January 22–27, 1951)

WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA AND
OTHER PHILADELPHIA INSTITUTIONS

THE AMERICAN COLLEGE OF PHYSICIANS
4200 PINE STREET
PHILADELPHIA 4, PA.

WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., *Director*

(Minimal Registration, 50;
Maximal Registration, 75)

Fees: A.C.P. Members, $30.00
Non-members, $60.00

Consulting Committee

THOMAS M. MCMILLAN, M.D., F.A.C.P.
EDWARD L. BORTZ, M.D., F.A.C.P.
CHARLES C. WOLFERTH, M.D., F.A.C.P.
CHARLES L. BROWN, M.D., F.A.C.P.
WILLIAM D. STROUD, M.D., F.A.C.P.
MARY H. EASBY, M.D., F.A.C.P.
SAMUEL BELLET, M.D., F.A.C.P.
THOMAS M. DURANT, M.D., F.A.C.P.

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C. J. VAN SLYKE, M.D., Director, National Institutes of Health, Bethesda, Md.

S. O. WAIFE, M.D., Assistant Director in Charge of Medical Education, Philadelphia General Hospital; Instructor in Medicine, Woman's Medical College of Pennsylvania; Philadelphia, Pa.

EDWARD WEISS, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine; Director of Research in Psychosomatic Medicine, National Committee for Mental Hygiene; Philadelphia, Pa.

PAUL D. WHITE, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Executive Director, National Advisory Heart Council, and Chief Consultant, National Heart Institute; Boston, Mass.

CHARLES C. WOLFERTH, M.D., F.A.C.P., Professor of Medicine and Administrator of Robinette Foundation, University of Pennsylvania School of Medicine, Philadelphia, Pa.

FRANCIS C. WOOD, M.D., F.A.C.P., Professor of Medicine and Chairman of the Department, University of Pennsylvania School of Medicine, Philadelphia, Pa.

WALLACE M. YATER, M.D., F.A.C.P., Director of Yater Clinic, Washington, D. C.; Formerly Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine; Washington, D. C.

LAURITZ S. YLVISAKER, M.D., F.A.C.P., Vice-President and Medical Director, Fidelity-Mutual Life Insurance Company; Chairman, Committee on Rehabilitation, Philadelphia Heart Association; Philadelphia, Pa.

HAROLD A. ZINTEL, M.D., F.A.C.S., Assistant Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa.

OUTLINE OF COURSE

Monday, January 22

A.M. Session

9:00– 9:10 Introductory Remarks and Announcements.
DR. LEAMAN.

9:10–10:00 Psychosomatic Aspects of Cardiovascular Disease.
DR. WEISS.

10:00–11:00 Angiocardiography.
DR. DOTTER.

11:00–11:15 Intermission.

11:15–12:30 Cardiac Catheterization.
DR. BING.

P.M. Session

2:00– 3:00 Recent Developments in the Diagnosis and Treatment of Congenital Cardiac Defects.
DR. DEXTER.

3:00– 3:30 QUESTION AND ANSWER PERIOD. Diagnosis and Treatment of Congenital Lesions.
DRS. BING, DEXTER AND DOTTER.

3:30– 3:45 Intermission.

3:45– 4:30 Clinical Value of Phonocardiography.
DR. SPRAGUE.
4:30– 5:15 The Relative Value of the History and Physical Examination in the Diagnosis and Treatment of Heart Disease.
DR. WHITE.
6:30. RECEPTION AND DINNER for Members of the Course and their Wives at the Penn-Sheraton Hotel, 39th and Chestnut Streets.

Tuesday, January 23

A.M. Session
9:00– 9:30 Treatment of Shoulder-Hand Syndrome Following Myocardial Infarction.
DR. NAIDE.
9:30– 10:45 Management of the Cardiac Patient from the Standpoint of the Anesthesiologist.
DR. DRIPPS.
10:45–11:00 Intermission.
11:00–12:30 Round Table. The Heart in Surgery and Pregnancy. The Surgical Risk.
DRS. DRIPPS, EASBY, JOHNSON, WOOD, RAVDIN, MONTGOMERY.

P.M. Session. SYMPOSIUM ON TREATMENT OF CONGESTIVE FAILURE.
2:00– 2:30 Mechanisms in Congestive Failure.
DR. LEITER.
2:30– 3:15 Digitalis Preparations.
DR. DEGRAFF.
3:15– 3:30 Intermission.
3:30– 4:30 Other Aspects of Treatment.
DR. DURANT.
4:30– 5:45 QUESTION AND ANSWER PERIOD.
DRS. DURANT, LEITER, DEGRAFF, STARR, PERERA.

Wednesday, January 24

A.M. Session
9:00– 9:30 Differential Diagnosis between Cardiac and Pulmonary Disease by Pulmonary Function Tests.
DR. COMROE.
9:30–10:30 PULMONARY HEART DISEASE. Panel Discussion.
DRS. COURNAND, LONG AND KOSSMANN.
10:30–10:40 Intermission.
10:40–11:30 Modern Trends in Electrocardiography.
DR. KATZ.
11:30–12:45 QUESTION AND ANSWER PERIOD. Electrocardiography.
DRS. KATZ, GOLDBERGER, BELLET, MCMILLAN.

P.M. Session. SYMPOSIUM ON RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE.
2:00– 2:30 Modern Concepts Regarding Collagen Diseases.
DR. EHRICH.
2:30– 3:00 Present-Day Trends in Therapy.
DR. HUBBARD.
3:00– 3:15 Intermission.
3:15– 4:15 Observations on the Value of Cortisone and ACTH in Acute Rheumatic Fever.
DR. BARNES.

4:15– 5:15 Question and Answer Period.
Drs. Ehrich, Hubbard, Barnes, Stroud, Brown, Stokes.

Evening Session

8:30 This meeting will be held in the Main Auditorium of the U. S. Naval Hospital. It will be a joint meeting of the Philadelphia Heart Association, the Section on General Medicine of the College of Physicians of Philadelphia, the Postgraduate Course in Cardiovascular Diseases of the American College of Physicians and the Staff of the U. S. Naval Hospital, Philadelphia.

Panel Discussion: Current Trends in the Treatment of Hypertension.
Indications for Medical Versus Surgical Treatment.
Dr. Wolferth.
Evaluation of New Therapeutic Agents.
Dr. Hafkenschiel.
Types of Surgical Treatment.
Dr. Zintel.
Management of the Complications of Hypertensive Cardiovascular Disease.
Dr. Kern.
Moderator: Dr. Love.

Thursday, January 25

A.M. Session

9:00– 9:50 The Use of Anti-coagulant Therapy in Heart Disease.
Dr. Vander Veer.

9:50–10:50 Bacterial Endocarditis. Diagnosis and Treatment.
Dr. Loewe.

10:50–11:00 Intermission.

11:00–12:15 Round Table. The Heart in Infections.
Drs. Loewe, LaBoccetta, Reimann, Flippin, Gefter, Edeiken, McMillan.

P.M. Session. Clinical Demonstrations at the Philadelphia General Hospital. Under direction of Drs. Schnabel and Waife.

2:00– 4:00 Cardiac Pathology, Applied Electrocardiography, Interpretation of Phonocardiographic Records, Cardiac Roentgenology, Electrokymography, Cardiac Catheterization and Bedside Demonstrations (rotating sections).

4:00– 5:00 Phonocardiographic Demonstration of Murmurs and Heart Sounds. (Patients from Medical Services.)
Dr. Bellet.

Friday, January 26

A.M. Session

9:00– 9:30 The Heart in Anemia.
Dr. Kay.

9:30–10:00 The Use of Isotopes in Cardiovascular Disease.
Dr. Kety.

10:00–10:45 Some Endocrine Disorders Affecting the Heart.
Dr. Rose.

10:45–11:00 Intermission.

11:00–12:30 A Review of Clinical Electrocardiography Including Treatment of Arrhythmias.
Drs. McMillan and Bellet.

P.M. Session

2:00– 2:45 Present Concepts Regarding Etiology and Management of Arteriosclerosis.
Dr. Dock.

2:45– 3:30 Treatment of the Cardiac Diabetic Patient.
Dr. Dillon.

3:30– 3:45 Intermission.

3:45– 5:00 Panel Discussion. What's Ahead in the Field of Cardiovascular Diseases?
Drs. Van Slyke, Ferree, Lucchesi, Connor and Mr. Betts.

Evening Session

8:00 "Information Please."
Drs. Margolies, McMillan, Naide, Leaman, Johnson, Bellet, Yater.

Saturday, January 27

A.M. Session

9:00– 9:30 Trauma and the Heart.
Dr. Gouley.

9:30–10:15 Treatment of Heart Disease in Geriatric Practice.
Dr. Bortz.

10:15–10:25 Intermission.

10:25–11:15 Trends in Present-Day Management of Coronary Disease.
Dr. Yater.

11:15–11:45 Rehabilitation of the Cardiac Patient.
Dr. Rusk.

11:45–12:30 Panel Discussion. Rehabilitation.
Drs. Rusk, Ylvisaker, LaPlace.

New Life Members, The American College of Physicians

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians, since the publication of the last issue of this journal:

Dr. H. Archibald Des Brisay, Vancouver, B. C., Canada
Dr. Homer Raymond Blincoe, New York, N. Y.

Gift to the College Library

Grateful acknowledgment is made to Dr. Franklin A. Kyser, F.A.C.P., Evanston, Ill., for the gift of a copy of his new book "Therapeutics in Internal Medicine," which was recently published by Thomas Nelson and Sons, New York, N. Y.

The College library is composed of the works of many Fellows of the College, who frequently present copies of their books, with the result that the library has become a living memorial to these Fellows.

Postgraduate Course in Cardiology

The Emory University School of Medicine has scheduled a postgraduate course in cardiology to be given March 5–9, 1951. It is designed for those physicians with special interest in cardiology and for internists who wish further preparation in the

field. Further information may be obtained by writing to Dr. Russell H. Oppenheimer, F.A.C.P., Director of Postgraduate Education, Emory University School of Medicine, Atlanta 3, Ga.

Washington University School of Medicine's Postgraduate Program

Washington University School of Medicine at St. Louis is expanding its program of postgraduate courses for the general practitioner and for specialists. From November 8 to 10, they offered a postgraduate course in Cardiology; from December 11 to 14, a course in Dermatology, and from November 30 to December 2, a course in Clinical Pathology for Medical Technicians. Information about future programs may be obtained from Dr. B. Eiseman, Assistant Dean.

The Forty-Seventh Annual Congress on Medical Education and Licensure will be held February 12–13, 1951, at the Palmer House, Chicago, Ill. The Congress will be under the auspices of the Council on Medical Education and Hospitals, A.M.A., and the Federation of State Medical Boards of the United States. Immediately preceding the Congress on February 11, an open meeting of the Advisory Board for Medical Specialties will be held.

Nobel Prize Winners

The 1950 Nobel Prize in medicine was awarded to Dr. Philip S. Hench, F.A.C.P., and Dr. Edward C. Kendall, both of the Mayo Clinic, Rochester, Minn., and Professor Tadeusz Reichstein of the University of Basel, Switzerland. In making this award on October 26, the Caroline Institute of Stockholm recognized the work these scientists have done on Cortisone and ACTH.

The actual presentation of the prize, which will be divided among the three winners, was made in Stockholm on December 10 in the most colorful ceremony since the Nobel Foundation was established 50 years ago. This was the 41st award in medicine under the terms of Alfred Nobel's will.

William Crawford Gorgas Selected for New York University Hall of Fame

Dr. William Crawford Gorgas, who was endorsed by the American College of Physicians and many other medical societies, received the highest number of votes of any of the candidates of the Hall of Fame of New York University and has so been selected. Electors of the Hall of Fame include 75 or more individuals consisting of university or college presidents, historians or professors of history or literature, scientists, authors, editors and artists, men and women of affairs, high public officials and justices, national or state.

It was William Crawford Gorgas who effectuated the conquest of yellow fever and the control of malaria and other tropical diseases during the construction of the Panama Canal in the early part of this century. Dr. Gorgas later became the Surgeon General of the United States Army and by special act of Congress was given the rank of Major General. He was offered the presidency of the University of Alabama. His Majesty King George V personally presented to him the insignia of Knight Commander of the Most Distinguished Order of St. Michael and St. George, and he was President of the American Medical Association in 1908–09. He died in London July 4, 1920.

Public Health Service Grants Funds for ACTH Research

The U. S. Public Health Service has appropriated $3,600,000 for research with the new drugs, cortisone and ACTH, into a number of diseases. The entire sum has been allocated for research grants to non-federal institutions and scientists. Grants will be made largely for the study of the compounds in relation to arthritis and cancer, mental and neurological, metabolic and cariovascular diseases, as well as for basic laboratory studies on the general biological effects of the compounds. Research projects on these diseases with which there is greatest chance for developing practical treatment procedures, or from which important fundamental information may be obtained, will be selected for special emphasis.

The Third Inter-American Congress on Brucellosis was held in Washington, D. C., November 6–10, under the joint sponsorship of the Inter-American Committee on Brucellosis, the United States Committee on Brucellosis and the Pan American Sanitary Bureau of the World Health Organization. The purpose of the Congress was to review the advances in research on brucellosis that have been made since the last Congress was held in 1948 in Argentina. Dr. Wesley W. Spink, F.A.C.P., Professor of Medicine at the University of Minnesota Medical School and Chairman of the United States Committee on Brucellosis, was elected President of the Inter-American Congress on Brucellosis at the November 7 session.

The Medical College of Virginia conducted a postgraduate course in Cardiology, during the two week period, October 23, through November 3. Forty-eight physicians attended the course. On the faculty were Dr. William Porter, F.A.C.P., Dr. Nathan Bloom, F.A.C.P., Dr. Reno R. Porter, F.A.C.P., Dr. Paul D. Camp, F.A.C.P., Dr. Wellford C. Reed, F.A.C.P., Dr. Armistead D. Williams (Associate), and Dr. Harold McCue.

The Memorial Hospital Intern's Alumni Association held the John F. Kenney Memorial Clinic Day at the hospital, Pawtucket, R. I., November 1, 1950. In addition to an all day clinical program, the meeting was addressed by the Governor of Rhode Island, The Honorable John O. Pastore. Dr. John F. Kenney was a Fellow of the American College of Physicians and had been connected with the Memorial Hospital of Pawtucket for many years. He died on March 20, 1950.

Dr. Frederick L. McDaniel, F.A.C.P., Richmond, Assistant to the Commissioner, Department of Mental Hygiene and Hospitals for the Commonwealth of Virginia, was recently appointed to the additional position of State Consultant for the Mental Hygiene Program in Virginia.

Dr. Harold J. Harris, F.A.C.P., New York City, has been appointed to the Panel of Experts on Brucellosis of the World Health Organization (United Nations), the first meeting of which was held in Washington, D. C., during and following the Third Inter-American Congress on Brucellosis during November, 1950.

Dr. Harris was a guest speaker on the subject "Diagnosis and Treatment of Brucellosis," before the Second Assembly of the American Academy of General Practice at Baltimore, Md., October 5, 1950.

Dr. J. Harry Murphy, F.A.C.P., Omaha, Nebr., was recently elected President of the Northwest Pediatrics Society.

The Miami Heart Association has announced the election of Dr. Victor H. Kugel, F.A.C.P., and Dr. Earl R. Templeton, F.A.C.P., both of Miami Beach, as President and President-Elect, respectively.

Dr. Russell L. Haden, F.A.C.P., recently Head of the Department of Medicine at the Cleveland Clinic, has been appointed Medical Director of the Red Cross National Blood Program. Dr. Haden will direct the medical aspects of the blood program as it is expanded to provide blood, plasma and other derivatives for the nation's hospitals and for military and civil defense needs.

Dr. Samuel A. Overstreet, F.A.C.P., Louisville, was recently installed as President of the Kentucky State Medical Association.

Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala., was the guest speaker at the annual meeting of the Kentucky Chapter of the American Rheumatism Association held in Louisville, September 27.

Free public lectures are being presented by the New York Academy of Medicine on the general subject "Medicine and Science." On January 31, Dr. Harold G. Wolff, F.A.C.P., New York, will speak on "Life Situations, Emotions and Bodily Disease."

At the meeting of the Chicago Medical Society on October 25, Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on "Abdominal Pain," and Dr. John H. Fitzgibbon, F.A.C.P., Portland, Ore., spoke on "Diseases of the Esophagus."

Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., will deliver the Alfred Friedlander Lecture on January 23, 1951 in connection with the scientific program of the Academy of Medicine of Cincinnati. His subject will be "A Plea for the Stethoscope."

Dr. Malcolm T. MacEachern, F.A.C.P., Director Emeritus of the American College of Surgeons and Professor of Hospital Administration at Northwestern University, was awarded an honorary degree of Doctor of Laws by McGill University at its Founders' Day Convocation on October 6.

In order to study problems pertaining to chronic diseases and to make recommendations to existing agencies and organizations, the State of Indiana has organized the Indiana Commission on Chronic Illness. Among those appointed to this commission by the governor is Dr. Leroy E. Burney, F.A.C.P., Indianapolis.

The Cascade County (Montana) Medical Society sponsored a Medical-Surgical Conference at Great Falls, October 9–10. Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., and Dr. Ferdinand R. Schemm, F.A.C.P., Great Falls, Mont., were among the guest speakers.

On November 2–4 the Division of Medical Sciences of the National Research Council arranged a symposium on burns at the request of the Research and Development Board, Department of Defense. The symposium was held in the National Academy of Sciences Building, Washington, D. C., and several speakers from outside the United States were on the program. Among these was Dr. John S. L. Browne, F.A.C.P., Montreal, Que., whose subject was "Stress, Injury and Endocrine Response."

Among the guest speakers at the annual meeting of the Southwestern Medical Association held in Phoenix, Ariz., October 26–28, were Dr. William Dock, F.A.C.P., Brooklyn, N. Y., "The Ballistocardiograph as an Aid in Management of Cardiac Problems in an Aging Population"; Dr. George Piness, F.A.C.P., Los Angeles, Calif., "Diagnosis and Management of Unusual Allergic Syndromes"; and Dr. Maxwell M. Wintrobe, F.A.C.P., Salt Lake City, Utah, "Effect of ACTH and Cortisone on the Hemopoietic System."

The First World Congress of Cardiology was held in Paris, September 3–9, during which 1,000 heart specialists from 55 countries agreed to form the International Society of Cardiology. Among those elected to office were Dr. Paul D. White, F.A.C.P., Boston, Mass., First Vice Chairman, and Dr. Ignacio Chavez, F.A.C.P., Mexico, D. F., Second Vice Chairman.

Dr. Edmund Jacobson, F.A.C.P., Chicago, Ill., addressed the Section on Physical Medicine of the New York Academy of Medicine on December 8, 1950, on the subject "Control of Early Hypertension by Progressive Relaxation."

The U. S. Air Force Medical Service held a joint conference on October 6–8 in Washington, D. C., for members of the National Medical Civilian Consultants and for surgeons from the major USAF Commands. The National Medical Civilian Consultants consists of approximately 30 nationally-known specialists under the chairmanship of Dr. W. Paul Holbrook, F.A.C.P., Tucson, Ariz. These consultants will meet with Major General Harry G. Armstrong, F.A.C.P., Surgeon General of the Air Force Medical Service. Among the subjects to be discussed will be the medical personnel situation; medical planning and mobilization, including the blood program; and biological defense activities.

At the recent Session of the Oregon State Medical Society in Gearhart, Dr. Blair Holcomb, F.A.C.P., and Dr. Robert F. Miller, (Associate), both of Portland, were named President-Elect and Secretary, respectively, for 1950–1951.

The Medical College of the State of South Carolina held its Annual Founders' Day Program on November 2. Dr. Kenneth M. Lynch, F.A.C.P., President and Professor of Pathology, conducted a pathology conference. At the banquet which concluded the program Dr. James H. Means, F.A.C.P., Boston, spoke on the subject "Physician, Know Thyself."

Seven Fellows of the American College of Physicians delivered papers at the Annual Convention of the Association of Military Surgeons of the United States

which was held November 9–11 in New York, N. Y. Among the speakers were: Dr. Louis H. Bauer, New York, "The World Medical Association"; Dr. Howard A. Rusk, New York, "Total Rehabilitation in Total Mobilization"; Captain Lloyd R. Newhouser, (MC), USN, "Practical Considerations of a Blood Program in a National Emergency"; Dr. Irving S. Wright, New York, "Use of Anticoagulants in Military Medicine"; Dr. Chester S. Keefer, Boston, "Selection of Antibiotics for Medical and Surgical Patients"; Dr. William D. Stroud, Philadelphia, "Optimism in Treatment and Prognosis of Cardiovascular Disease," and Dr. Leslie N. Gay, Baltimore, "A Supplementary Report on Dimenhydrinate (Dramamine)."

Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., is President-Elect of the Medical Society of New Jersey.

The Roosevelt Hospital, New York, N. Y., has established an allergy institute in honor of Dr. Robert A. Cooke, F.A.C.P., director of the hospital's allergy clinic since its inception in 1918. The institute is an outgrowth of the allergy clinic founded by Dr. Cooke and Dr. Albert Vander Veer. The institute is now being conducted in the old pavilion building of the hospital. Next year the Tower Memorial Building will be erected and an entire floor will be devoted to the institute's clinic and laboratories.

At the annual meeting of the Post Graduate Medical Assembly of South Texas held in Huston, November 20–22, the following Fellows of the College were among the speakers: Dr. William Dameshek, Boston, "Chemotherapy of Leukemia and Leukosarcoma"; Dr. O. Spurgeon English, Philadelphia, "Emotional Common Denominators in Psychosomatic Disease" and Dr. Howard B. Sprague, Boston, "Cardiac Arrhythmias."

Dr. William H. Sebrell, F.A.C.P., Bethesda, Md., has been appointed Director of the National Institutes of Health of the U. S. Public Health Service.

Dr. C. Lydon Harrell, F.A.C.P., Norfolk, was recently inducted as President of the Medical Society of Virginia.

OBITUARIES

DR. WALTER WALKER PALMER

Dr. Walter Walker Palmer, F.A.C.P., died in Tyringham, Massachusetts, on October 28, 1950. He was born in Southfield, Massachusetts, February 27, 1882, received his B.S. degree from Amherst College in 1905 and his M.D. degree from Harvard Medical School in 1910. Beginning in 1913 he served successive periods on the staffs of the Massachusetts General Hospital, The Rockefeller Institute for Medical Research in New York, Columbia University, and Johns Hopkins University School of Medicine. In 1921 he was appointed Bard Professor of Medicine at Columbia University College of Physicians and Surgeons, succeeding Dr. Warfield T. Longcope, F.A.C.P., who had resigned. He continued in this capacity until June, 1948, when he resigned and became Professor Emeritus.

DR. WALTER WALKER PALMER

Dr. Palmer had served as Chairman of the Medical Advisory Committee for the report to the President of the United States on a program for post-war scientific research, known as the Vannevar Bush report. During the last two years of World War I, Dr. Palmer served in the Medical Reserve Corps of the Army, and from 1926 to 1931, he was a Major in the Medical Reserve Corps.

Dr. Palmer was a member of many professional bodies, including the New York Academy of Medicine, the Harvard Society of New York (President, 1926–27), the American Society for Clinical Investigation, the Council on Pharmacy and Chemistry of the American Medical Association, the Harvey Society, the Association of American Physicians, and had been a Fellow of the American College of Physicians since 1928. He had a long and useful service in the American College of Physicians. He

served for several years as its Governor for Eastern New York and thereafter was a member of the Board of Regents and a member of many important committees. He served as President of the College for the year 1948–49. During the last two years, Dr. Palmer was Director of the Public Health Research Institute of the City of New York and Consultant in Medicine at Presbyterian Hospital. He was also Editor-in-Chief of Nelson's Loose Leaf System of Medicine. During World War II, he was Chairman of the Committee on Drugs and Supplies of the National Research Council. He was also Vice President of the Century Association of New York and a Diplomate of the American Board of Internal Medicine.

Dr. Palmer was a most distinguished physician whose long service in medicine, particularly as a teacher, will be long remembered. His passing constitutes a real loss to American medicine.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. THOMAS RICHARDSON BROWN

On September 26, 1950, Baltimore lost one of its outstanding medical advisors and investigators, as well as an able citizen. Dr. Brown had attained honors in Medicine, but he also won himself a place in the hearts of his fellow Baltimoreans to whom he was known by the familiar "Dr. Tom." He was born in Baltimore in 1872; was a graduate of Johns Hopkins University School of Medicine in 1897.

Dr. Brown was Assistant Physician and Associate in Medicine at Johns Hopkins Hospital from 1898 to 1919. He was later Associate Professor of Medicine at Johns Hopkins University School of Medicine, and Physician in Charge of the Division of Digestive Diseases of the Johns Hopkins Hospital. He was attending Physician at the Union Memorial and Bon Secours Hospitals, the Hospital for the Women, and the Church Home and Hospital. Later he became a Trustee of Johns Hopkins University and was Chairman of the Medical Advisory Board of the Alfred I. DuPont Institute of the Nemours Foundation.

Dr. Brown has written numerous medical books and articles which appeared throughout the medical journals of this country and abroad. In 1928 he was elected a Fellow of the American College of Physicians. He was a Diplomate of the American Board of Internal Medicine, a member of the American Gastro-enterological Association, and the Maryland Medical and Chirurgical Faculty. Dr. Brown had to retire in the last few years of his life because of ill health, yet during this period he never lost touch with his clinic and his many outside activities. His passing was a great loss to his innumerable friends in the medical profession.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. ROY RACHFORD KRACKE

Dr. Roy Rachford Kracke died suddenly of an acute coronary thrombosis on Tuesday, June 27, 1950. With the death of Dr. Kracke, The Medical College of Alabama lost the first dean of its new four-year medical school in Birmingham.

Dr. Kracke was born in Hartselle, Ala., on December 5, 1897. He was graduated from the University of Alabama in 1924 and received his M.D. degree from Rush Medical College in 1928. Following completion of his formal training at the U. S. Naval Hospital in Brooklyn, N. Y., Dr. Kracke served successively as Assistant Professor, Associate Professor and Professor of Pathology, Bacteriology and Laboratory Diagnosis at Emory University in Atlanta. With the conversion of The

Medical College of Alabama from a two-year to a four-year school and its movement to Birmingham, Dr. Kracke accepted the responsibilities of Dean and Professor of Clinical Medicine on August 1, 1944, where he remained until his death. Here he gave wholeheartedly of his time and energy, and his unusual foresight and ability are evident today in the progress made by The Medical College of Alabama since 1944.

Dr. Kracke's prime interest was hematology and some of his earliest contributions won him international recognition. His studies on agranulocytosis have, no doubt, been responsible in preventing numerous deaths due to the continued use of certain compounds, such as aminopyrine. He was a constant contributor to medical and scientific literature and wrote nearly ninety papers on his hematological observations. He was also the author of the following books: "Diseases of the Blood," "Color Atlas of Hematology," "Textbook of Clinical Pathology," and "Laboratory Manual of Bacteriology."

In 1933 the Medical Association of Georgia awarded him the Hardeman Cup for medical research. In 1934 Dr. Kracke was awarded a certificate of merit by the American Medical Association for his scientific exhibit, and in the same year he received the Ward-Burdick gold medal from the American Society of Clinical Pathologists. The University of Chattanooga conferred the honorary degree, LL.D., on him in 1946.

Dr. Kracke's affiliations were many. At the time of his death he was Vice-Chairman of the Medical Advisory Council to the Veterans Administration; a member of the Board of Medical Consultants, Oak Ridge Institute of Nuclear Studies and a member of the Hematology Study Section, U. S. Public Health Service. He had served as President of the American Society of Clinical Pathologists; Chairman of the Pathology Section of both the American Medical Association and the Southern Medical Association; and as Director of the Hematological Registry of the American Society of Clinical Pathologists. He had been a Fellow of the American College of Physicians since 1949. He was a member of the Postdoctoral Fellowship Board, National Academy of Sciences and a Diplomate of the American Board of Pathology. Dr. Kracke had membership in the following: American Medical Association, Southern Medical Association, American Society of Clinical Pathologists, Society of Experimental Biology and Medicine, Medical Association of Alabama, Jefferson County Medical Society of Alabama, Georgia Academy of Science, Alabama Academy of Science, Society of the Sigma Xi, Phi Beta Kappa, Alpha Omega Alpha and various civic organizations.

Dr. Kracke's unusual kindness, intelligence, honesty and humor endeared him to professional and lay people alike. His ideals were always high and he set an excellent example for those he worked with and taught.

Dr. Kracke will be greatly missed, but we are all grateful for the opportunity of having been associated with him. His memory will be cherished.

E. Dice Lineberry, M.D., F.A.C.P.,
Governor for Alabama
William H. Riser, Jr., M.D. (Associate)

DR. BURT R. SHURLY

Burt Russell Shurly, a Fellow of the American College of Physicians since 1921, died October 20, 1950, in Detroit. Dr. Shurly was born in Chicago, Ill., on July 4, 1871. He received his academic degree at the University of Wisconsin, where he graduated in 1894. He received his M.D. degree from the Detroit College of Medicine and Surgery in 1895. He later had postgraduate studies at the University of Vienna Faculty of Medicine. For many years Dr. Shurly was Professor and Director of Otolaryngology, Wayne University College of Medicine. He had been

a consultant at the Harper, City of Detroit Receiving and Woman's Hospitals, and the Detroit Orthopedic Clinic. He was Chief of Staff of the Shurly Eye, Ear, Nose and Throat Hospital, and attending physician of the Detroit Tuberculosis Sanatorium.

Dr. Shurly served in the Spanish-American War and in World War I. In the former he was a Medical Corpsman in the Navy. During World War I he served in France in the U. S. Army, Medical Corps, with the rank of Lieutenant Colonel, as Commanding Officer and Medical Director of Base Hospital 36. At the outset of World War II, even though Dr. Shurly was 70 years of age, he endeavored to be reinstated to active duty in the Medical Corps.

Dr. Shurly's medical associations were many. He was a member and past president of the American Laryngological Society and a member and past president of the American Laryngological, Rhinological, and Otological Society. He was also a member and past president of the American Academy of Ophthalmology and Otolaryngology, a member of the American Clinical and Climatological Association and a Fellow of the American College of Surgeons. His civic activities were many, including the presidency of the Detroit Board of Education and membership on the Detroit Public Library Commission.

His loss will be felt in many ways in this community.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. DUDLEY C. SMITH, SR.

Dudley Crofford Smith, Sr., B.S., M.D., F.A.C.P., was born in Lafayette, Miss., December 15, 1892, and died on August 30, 1950, at Charlottesville, Va., of coronary thrombosis. Graduate of University of Mississippi, B.S., 1914; University of Virginia, Department of Medicine, M.D., 1917. Began teaching in the University of Virginia as Instructor in 1919 and continued actively on the faculty until he was made Professor of Dermatology and Syphilology and Head of the Department, which position he held at his death.

He was a Diplomate of the American Board of Dermatology and Syphilology and was a member of the American Dermatological Association, of which he was Vice President in 1935. He was a member of the American Association for the Advancement of Science, the Society of Investigative Dermatology, the Atlantic Dermatologic Conference and the American Academy of Dermatology and Syphilology. He was elected chairman of the same section of the Southern Medical Association. He was Past President of the Albemarle County Medical Society and of the Baltimore-Washington Dermatological Society.

He had been a Special Consultant for the U. S. Public Health Service for years and aided in the standardization of the treatment of syphilis with penicillin.

Dr. Smith was one of the outstanding members of the Faculty of the School of Medicine of the University of Virginia, and had keen interest in his interne and resident staff and particularly in graduate teaching. He was an able physician as well as an outstanding dermatologist and contributed many valuable articles to the literature of his specialty.

Dr. Smith was esteemed and admired by colleagues, students and a large circle of friends. His chief avocation was fishing, enjoying nothing better than a fishing trip with his friends.

His sudden death removes from medicine an outstanding leader, an effective teacher and an energetic researcher. His professional influence and his warm, kindly spirit will remain active for years to come.

CHARLES M. CARAVATI, M.D., F.A.C.P.,
Governor for Virginia

DR. HENRY JOHNSON ULLMANN

Dr. Henry Johnson Ullmann, F.A.C.P., was born at Evanston, Ill., in 1881. He received his B.S. from the University of Chicago in 1910 and his M.D. from Rush Medical College in 1912. He was associated with Rush Medical College until 1920 and was radiologist at St. Joseph's and Children's Memorial Hospitals in Chicago. Soon thereafter, he removed to Santa Barbara, Calif., and became Director of the Department of Cancer Research at the Santa Barbara Cottage Hospital, a connection he held for many years, leading up to his last appointment as Director of the Memorial Foundation of that institution. He was a diplomate of the American Board of Radiology, a member of the Los Angeles Cancer Society, American Roentgen Ray Society, American Radiological Society, Santa Barbara County Medical Society, California State Medical Society and the American Association for the Advancement of Science, and a Fellow of the American Medical Association and the American College of Radiology. He had been a Fellow of the American College of Physicians since 1928. He was the author of many contributions in the field of radiology and cancer. During the First World War he served in the Medical Corps of the Army and thereafter held a reserve commission as a Lieutenant Colonel.

Dr. Ullmann's death was a tragedy. On October 15, 1950, he was in flight in a single-engined plane with his son, Henry, Jr., and his son's wife and the pilot, when they attempted an emergency, instrument landing and apparently overshot the field and were lost in the ocean. An intensified search by air and sea was unsuccessful in finding any of the party.

DR. VICTOR FELSENTHAL WOOLF

Dr. Victor Felsenthal Woolf, F.A.C.P., died October 16, 1950. He graduated from Columbia College in 1924 and from Columbia University College of Physicians and Surgeons in 1930. Since his graduation, he had been associated with Columbia University as an Instructor in Medicine. He was also associated with Bellevue, Lenox Hill and Sydenham Hospitals, and for the last few years had been Chief of the Tuberculosis Service of the Veterans Administration Hospital on Staten Island.

Dr. Woolf was a Fellow of the New York Academy of Medicine, a member of the American Trudeau Society and of the New York Society of Thoracic Surgery. He was a diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1949.

Just prior to his death, Dr. Woolf resigned his service with the Veterans Administration and re-associated himself with the Tuberculosis Service at Bellevue Hospital and Columbia University College of Physicians and Surgeons, and at the time of his death he was an Associate Visiting Physician at Bellevue Hospital and an Instructor in Medicine at Columbia University.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York

DR. SALING SIMON

Dr. Saling Simon, a well-known Denver internist, died on August 4, 1950.

Dr. Simon was born in New York City, June 5, 1870. He took his A.B. degree in 1889 from the College of the City of New York and his M.D. degree in 1895 from the Gross Medical College of Denver. Between the years of 1908 and 1914 Dr. Simon did postgraduate study at the Frederick William University Faculty of Medicine, Berlin; St. Mary's Hospital Medical School, London; University of Vienna Faculty of Medicine, Vienna; and University of Hamburg Faculty of Medicine, Hamburg.

Dr. Simon became a Fellow of the American College of Physicians on March 4, 1928. He was a member of the American Medical Association and the Denver and Colorado Medical Societies. He was certified by the American Board of Internal Medicine.

For many years Dr. Simon served on the faculty of the Gross Medical College. He was a Captain in the U. S. Army Medical Corps during World War I and during World War II he served as a consultant to the Colorado Selective Service Board. Throughout Dr. Simon's professional life he was closely identified with the staff activities of the Mercy, Presbyterian and Beth Israel Hospitals.

One of Dr. Simon's most important interests and activities centered around the National Jewish Hospital. He was the first secretary of the Medical Advisory Board of this institution (1899) and served as its medical director in 1917 and 1918. For many years he served as Vice Chairman of the Medical Advisory Board, and at the time of his death he had been an Honorary Chairman for a number of years.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado

DR. ESLIE HARTMAN

Dr. Eslie Hartman was born in Mt. Vernon, N. Y. on February 2, 1916. She received her A.B. degree in 1938 from the Washington Square College of New York University, and four years later received her M.D. degree from the College of Medicine of the same University.

In 1942 she came to Chicago, where she was affiliated with the University of Illinois College of Medicine and its Research and Educational Hospitals until the time of her death. She served first as interne, then as Resident in Medicine, and later as Instructor in Medicine and as Medical Consultant in the University Health Service. She was also a member of the staff of the Illinois Masonic Hospital and of the Chicago Fresh Air Hospital.

Since 1949 she had been an Associate of the American College of Physicians. She was a Diplomate of the National Board of Medical Examiners; a member of the Chicago Medical Society, the Illinois State Medical Society, the American Medical Association and the American Medical Women's Association.

Dr. Hartman's tragic death in an air crash near Erie, Pa., on July 13, 1950, caused a loss even more grave than the ending of her important research on the treatment of tuberculosis. It deprived patients and fellow physicians, alike, of a member of our profession who treated her patients not merely with a profound grasp of the science of medicine, but also with an extraordinary insight, sympathy and understanding. In Dr. Hartman there was an instinctive union between the science and art of medicine. By her very nature it was impossible for her to think of any patient as simply a collection of pathologic organs.

FREDERICK C. LENDRUM, M.D., Ph.D.

DR. MELVILLE WALLACE HUNTER

It is sad irony that Dr. Melville W. Hunter, F.A.C.P., should die of coronary arteriosclerosis soon after relinquishing the Presidency of the Louisiana Heart Association, a newly formed organization to which he had devoted much of his time and vigor. He died at his home in Monroe, Louisiana, on July 20, 1950, at the age of 50, a competent and widely respected physician.

Dr. Hunter was born in New Orleans on September 28, 1900. He graduated from Tulane University of Louisiana School of Medicine in 1925. He was a Fellow

of the American Medical Association, a Charter Member of the Louisiana Diabetic Association, a Charter Member, Director and Past President of the Louisiana Heart Association, and had been a Fellow of the American College of Physicians since 1935. He held appointments as Visiting Physician and Chief of Medicine of the E. A. Conway Memorial Hospital, Visiting Physician and member of the Medical Advisory Board of the St. Francis Sanitarium and Visiting Physician of the Riverside Sanitarium.

THOMAS FINDLEY, M.D., F.A.C.P.,
Governor for Louisiana

DR. PATRICK E. BIGGINS

Patrick E. Biggins, M.D. (Associate), Sharpsville, Pa., died August 19, 1950. He was born in 1880 and graduated in medicine from the Medico-Chirurgical College of Philadelphia in 1907. For many years he was a member of the staff and Cardiologist, Christian H. Buhl Hospital, Sharon, Pa. During World War I, he served in the Medical Corps of the U. S. Army with the rank of First Lieutenant. He was a Past President of the Association of Surgeons of the Pennsylvania Railroad. He was elected to the American Congress on Internal Medicine in 1924, from which his Associateship in the American College of Physicians originated. He is survived by four sons and three daughters—one son is Dr. James A. Biggins, who is in practice in Sharpsville.

Dr. Biggins was a man of outstanding character, highly respected by his contemporaries and the community and will be greatly missed by all.

CHARLES W. MORTON, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. JOHN VINCENT SMITH

John Vincent Smith, M.D., F.A.C.P., Perth Amboy, N. J., died at his office of coronary thrombosis on July 14, 1950, at the age of 62. He was born in Perth Amboy, Middlesex County, N. J., August 3, 1888.

Dr. Smith graduated from Long Island College of Medicine in 1912. He was for many years on the staff of the Perth Amboy General Hospital and was City Physician from 1923 to 1926. He was elected to two terms on the City Commission, serving as Commissioner of Public Works from 1926 to 1934. He was appointed by Governor Woodrow Wilson to single terms as Physician of the Port of Perth Amboy and as New Jersey State Public Health Officer.

Dr. Smith was a member of the American Medical Association, the American Heart Association, the Medical Society of New Jersey and the Middlesex County Medical Society. He became a Fellow of the American College of Physicians in 1931.

In his passing the community lost a worthy diagnostician and heart specialist, a wise administrator and a benevolent friend.

EDWARD C. KLEIN, JR., M.D., F.A.C.P.,
Governor for New Jersey

DR. PERCY BROWN

Percy Brown, M.D., F.A.C.P., was born in Cambridge, Mass., November 24, 1875, and died at Egypt, Mass., October 8, 1950. He came directly to the Harvard Medical School without formal college training and received his medical degree there in 1900. At once he became interested in radiology and was one of the pioneers, who paid a heavy price for developing knowledge in this field.

His first academic position at Harvard was in 1909, as Assistant in the use of the roentgen-ray. He served as Instructor in Roentgenology in his medical school from 1917 until he resigned in 1922. He was on the staff of various hospitals; he served during the First World War in the Medical Corps of the Army and was an active and greatly loved member of Base Hospital V (Harvard Unit). At the end of the War, he was discharged with the rank of Major.

He retired from active practice in 1934, suffering increasingly from the complications of improper protection against x-rays in his early and exploring days. He was elected a Fellow of the American College of Physicians in 1920. He was a Fellow of the American Medical Association, a diplomate of the American Board of Radiology and a past President of the American Roentgen Ray Society.

Dr. Brown was liked and respected equally by colleagues in his specialty and by colleagues throughout the entire range of medicine. He was an idealist, devoutly loyal to his friends and to his country; he was the kind of physician whose loss will always be felt by many people.

REGINALD FITZ, M.D., F.A.C.P.

DR. FRED MILLER DRENNAN, SR.

Dr. Fred Miller Drennan, Sr., F.A.C.P., died suddenly on August 26, 1950, from a recurrent coronary occlusion. Born on June 20, 1884, in Shelby County, Missouri, Dr. Drennan obtained his B.S. and M.S. degrees from the University of Chicago, and in 1913 his M.D. degree from Rush Medical College. During his academic days Dr. Drennan was an Associate Professor of Physiology in the University of Chicago. After interneships in the Presbyterian and Cook County Hospitals of Chicago, Dr. Drennan became an Assistant Professor of Medicine at Rush Medical College, a post he occupied until 1924 when he was appointed Associate Clinical Professor of Medicine at Loyola University School of Medicine; in 1928 he was promoted to Clinical Professor of Medicine. From 1915 to 1924 Dr. Drennan was an Associate of Dr. Bertram Sippy and a Member of the Staff of Presbyterian Hospital. He became associated with the Mercy Hospital of Chicago in 1924, being appointed Senior Attending Physician in 1928. He held various responsible positions in the Mercy-Loyola University Clinics and on the Loretto Hospital Board. In World War II he was Chairman of Medical Advisory Board No. 3 in Chicago.

Dr. Drennan was a member of the Chicago Society for Internal Medicine, the Chicago Medical Society, the Illinois State Medical Society, a Fellow of the American Medical Association, a Diplomate of the American Board of Internal Medicine, and since 1934 a Fellow of the American College of Physicians. His civic interests and responsibilities were evident from his participation in the work of the Boy Scouts, the P.T.A., and the Athletic Department of the High School.

Dr. Drennan was an unusually cheerful, genial, and charming person. As a physician and as a consultant, his services were valued highly. Fred will be sorely missed by his many friends, his loyal patients, and his devoted family. He is survived by Olive Clay Drennan whom he married in 1917, and by his sons, Fred Miller Drennan, Jr., and Dr. William Clay Drennan.

WALTER L. PALMER, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. JAMES NESTER O'BRIEN

James Nester O'Brien, M.D., Harrisburg, Pa., an Associate of the American College of Physicians since 1947, died June 10, 1950, of heart disease. He was born at Wheeling, W. Va., December 4, 1905, received his Bachelor of Science Degree in 1928 and his Medical Degree in 1930 from Georgetown University, Washington, D. C.

He interned at the Mercy Hospital, Pittsburgh, Pa., and did postgraduate work at the University of Pennsylvania Graduate School of Medicine and the Mayo Clinic. He had been a member of the Medical Staff of the Harrisburg Hospital since 1932. He saw active service in the Medical Corps of the United States Army in Africa and Italy and was later stationed in England.

Dr. O'Brien was a member of the Dauphin County Medical Society, the Pennsylvania State Medical Association, the Harrisburg Academy of Medicine and a Fellow of the American Medical Association.

DR. CHRISTIAN W. JANSON

Dr. Christian W. Janson, F.A.C.P., 71 years of age, specialist in the field of gastro-enterology, died in his Brooklyn home on September 15, 1950. He was a native of Brooklyn and practiced in the Bushwick section since his graduation from Cornell University Medical College in 1902. He was a member of Omega Epsilon Phi, medical fraternity, Kings County Medical Society and the Medical Society of the State of New York. He has been a Fellow of the American College of Physicians since 1923. He had retired recently as an Attending Gastro-enterologist at Wyckoff Heights Hospital.

Dr. Janson was past Grand Steward of the Grand Lodge of New York and past Deputy Grand Master of the 2nd Masonic District of Kings County, and held other offices in this organization.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York

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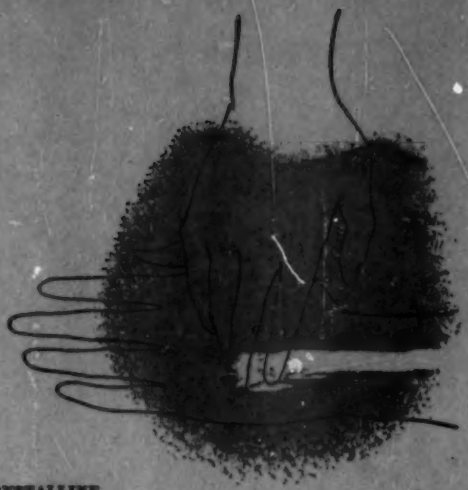

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